

Complementary Chinese Herbal Medicine Treatment is Associated with a Reduction of Surgical Rate in Patients with Dysfunctional Uterine Bleeding: A Propensity-Score Matched Cohort Study

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Background: Many patients with dysfunctional uterine bleeding (DUB) seek traditional medicine consultations. This study intended to investigate the association of complementary Chinese herbal medicine (CHM) with the surgery rate in patients with DUB in Taiwan.

Methods: We enrolled 43,027 patients with newly diagnosed DUB (ICD-9-CM codes 626.8) from the National Health Insurance Research Database in Taiwan during the period of 1997 to 2010. Among them, 38,324 were CHM users, and 4703 did not receive CHM treatment. After performing a 1:1 propensity-score match based on patients' age (per 5 years), comorbidities, conventional drugs, childbirth status, duration from the diagnosis year of DUB and index year, there were an equal number (n=4642) of patients in the CHM cohort and non-CHM cohort. The outcome measurement was the comparison of incidences of surgical events, including hysterectomy and endometrial ablation, in the two cohorts before the end of 2013.

Results: CHM users had a lower incidence of surgery than non-CHM users (adjusted HR 0.27, 95% CI: 0.22–0.33). The cumulative incidence of surgery was significantly lower in the CHM cohort during the follow-up period (Log rank test, $p < 0.001$). A total of 146 patients in the CHM cohort (4.99 per 1000 person-years) and 485 patients in the non-CHM cohort (20.19 per 1000 person-years) received surgery (adjusted HR 0.27, 95% CI: 0.22–0.33). CHM also reduced the risk of surgery in DUB patients with or without comorbidities. Regardless of childbirth status or whether patients took NSAIDs, tranexamic acid or progesterone, fewer patients in the CHM cohort underwent surgery than in the non-CHM cohort. The most commonly prescribed single herb and formula were Yi-Mu-Cao (Herba Leonuri) and Jia-Wei-Xiao-Yao-San, respectively.

Conclusion: The real-world data revealed that CHM is associated with a reduced surgery rate in DUB patients. This information may be provided for further clinical investigations and policy-making.

Keywords: complementary and alternative medicine, Chinese herbal medicine, dysfunctional uterine bleeding, hysterectomy, National Health Insurance Research Database, surgery

Introduction

Dysfunctional uterine bleeding (DUB) is defined as abnormal bleeding (in terms of the frequency, duration, and amount of bleeding) without any clear structural or systemic etiology identified. It is a common problem in women of reproductive age. Approximately 30% of women encounter the problem of abnormal uterine bleeding annually, and 25% of gynecologic surgeries are performed to treat this condition.¹ Furthermore, approximately 30–40% of hysterectomies are performed for the treatment of severe dysfunctional bleeding.² Uterine bleeding has a substantial impact on women's quality of life and may have a negative impact on healthcare costs as well as an associated loss of productivity.³ Overall, it has significant effects on the medical, socioeconomic, and psychological well-being of women.

Medical treatments such as NSAIDs, oral contraceptive pills, progestin, danazol, GnRH agonists, and anti-fibrinolytic drugs are used to reduce menstrual flow.^{4,5} Symptom recurrence after discontinuing the treatment is considered the main disadvantage of the medical therapies. The associated side effects and the necessity for long-term medical treatment may lead to patients' noncompliance during prolonged medical therapy, which is a factor influencing the decision of surgical management. If these pharmacological options are unsuccessful, surgical procedures of hysterectomy or the levonorgestrel intrauterine system (LNGIUS) (Mirena) are used.⁶ Hysterectomy causes complete cessation of menstruation, leading to complete control of the bleeding symptom. However, it requires considerable recovery time and is an expensive, invasive, and irreversible treatment procedure.⁷ In addition, hysterectomy may involve post-operative complications including hemorrhage, injury to adjacent organs such as the intestines and bladder, febrile morbidity, life-threatening events, urinary retention, urinary tract infections (UTIs), and wound infections.⁸ The most frequent long-term problems reported after surgery include fistula, chronic pain, bladder or bowel dysfunction, early menopause, sexual dysfunction, poor appetite, constipation, back pain, urinary problems, and psychiatric disturbance.⁹ Admission to hospital for hysterectomy not only impacts the daily activities of the patients but also extends to patients' families and their employers.¹⁰ Because surgery may result in long-term complications, negative quality of life, and significant social or economic costs, some women affected by DUB may seek complementary therapies such as traditional Chinese medicine (TCM) consultations in Taiwan.¹¹

In Taiwan, both conventional Western medicine and TCM are quite popular and considered as mainstream therapies for gynecological disorders.^{11–15} The National Health Insurance program reimburses both treatments.¹⁶ From the perspective of Chinese medicine theory, DUB is described as “Ben Lou” in TCM literature. It is regarded as “flooding and spotting” as a disruption of the harmony of Qi and Blood, which could be caused by “Blood Heat”, “Blood Stasis” and “Organ Dysfunction (Spleen, Liver and Kidney)”, and eventually leads to “Blood/Yin Deficiency”.¹¹ TCM views DUB as a sign of the body's internal imbalance and the treatments aim to harness the balance of “Yin and Yang” in the body through a combination of herbal medicine, acupuncture, dietary changes, and lifestyle modifications. While this theory fits some of the pathomechanisms of DUB, it is also important to point out that gynecological surgeries also play an important role in clinical management. We therefore are curious about whether there is a space to integrate TCM treatment in the management of DUB. In the meantime, the advantage of complementary TCM among patients of DUB in real-world clinical settings needs some substantial evidence.

We previously illustrated the prescription patterns and core prescriptions of Chinese herbal medicine (CHM) for patients with DUB.¹¹ Yi-Mu-Cao (Leonuri Herba) and Jia-Wei-Xiao-Yao-San were the most commonly prescribed single herb and herbal formula for patients with DUB in Taiwan. In this study, we aimed to investigate the relationship between surgery rate and complementary CHM treatment in patients with DUB. This could help determine the effects of TCM for patients with DUB and provide valuable information for clinical gynecologists.

Methods

Data Sources

The National Health Insurance (NHI) program was established in Taiwan in 1995. The program is highly representative of Taiwan's general population because the reimbursement policy is universal and mandatory. It covered more than 99% of Taiwanese residents. The data source of our study was the Longitudinal Health Insurance Database 2000 (LHID 2000), a real-world data derived from the National Health Insurance Research Database (NHIRD).¹⁷ The LHID 2000 contains

all the original claims data of 1 million beneficiaries randomly sampled from the registry of all beneficiaries in 2000.¹⁷ We conducted a nationwide, population-based, 1:1 propensity score-matched cohort study by analyzing data derived from the LHID 2000. The sampled patients exhibited no significant differences in age, birth year, or average insured payroll-related costs compared to the general population. We acquired the diagnostic codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taiwan (CMUH104-REC2-115).

Study Population

Patients newly diagnosed with dysfunctional uterine bleeding (ICD-9-CM code 626.8) ($n=51,354$) with at least 2 claims from January 1, 1997, to December 31, 2010, were selected from the database (Figure 1). The exclusion criteria included age younger than 18 years, incomplete information on age and sex, and withdrawal from the NHIRD during the follow-up period. Patients who received hysterectomy or endometrial ablation before the diagnosis of DUB were also excluded. To exclude the non-DUB reasons for hysterectomy, patients with a diagnosis of cervix uteri cancer (ICD-9-CM: 180.9, 233.1; A code: A120, A16), endometrial cancer (ICD-9-CM: 182), ovarian cancer (ICD-9-CM: 183, A code: A123), leiomyoma (ICD-9-CM: 218, A code: A152), and endometriosis (ICD-9-CM: 617) within 3 months before or after the diagnosis of DUB were also excluded. Finally, 43,027 patients with newly diagnosed DUB were included.

Patients who received CHM from their initial diagnosis of DUB to December 31, 2010, were identified as the CHM users ($n=38,324$). Those who never received CHM during the same period were identified as non-CHM users ($n=4,703$). Propensity score matching was used to select a comparable CHM group and non-CHM group. We performed a 1:1 propensity-score match based on each subject's age (per 5 years), comorbidities, drugs used, childbirth status, duration from the diagnosis year of DUB and index year through multiple logistic regression analysis to reduce the selection bias. Ultimately, equal numbers ($n=4,642$) of patients in the CHM group and non-CHM group were analyzed and followed up until December 31, 2013.

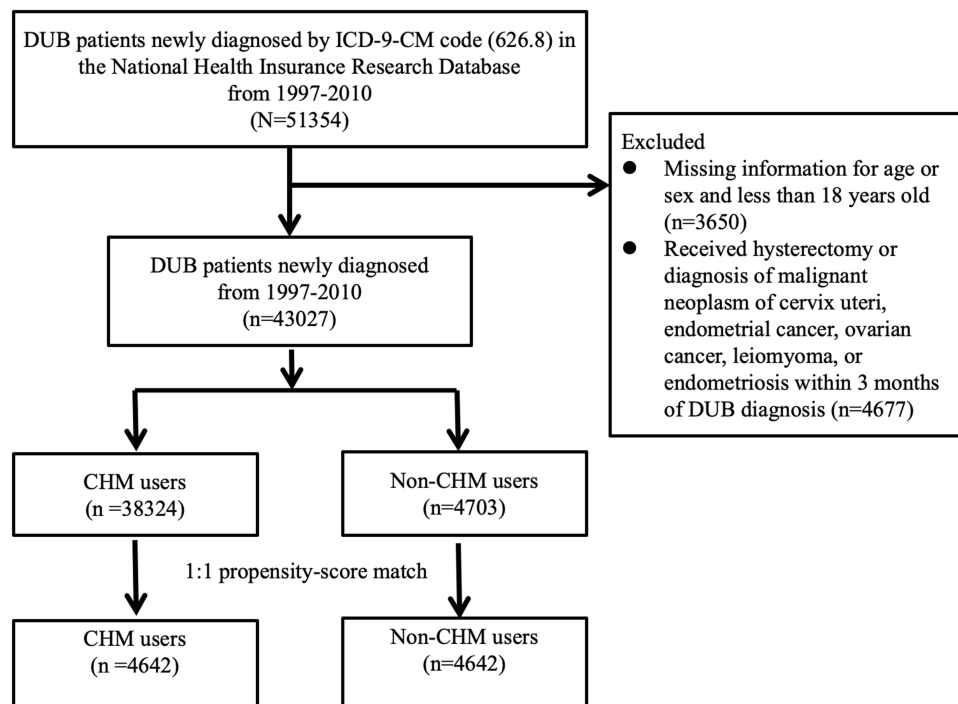


Figure 1 Flow recruitment chart. We identified the newly diagnosed dysfunctional uterine bleeding (DUB) patients from 1997 to 2000 from one million randomly selected subjects of the Longitudinal Health Insurance Database 2000 (LHID 2000) in Taiwan. After excluding patients according to the excluding criteria, we included 43,027 patients and separated them into CHM users ($n=38,324$) and non-CHM users ($n=4,703$) according to whether they received TCM treatment or not after the initial diagnosis of DUB. After performing 1:1 propensity score matching, there were 4642 patients in the CHM and non-CHM cohorts.

Covariate Assessment

Baseline comorbidities were considered present if ICD-9-CM codes appeared two or more times in outpatient or inpatient claims before the initial diagnosis of DUB, which included dysmenorrhea (ICD-9-CM: 625.3), inflammatory disease of ovary (ICD-9-CM: 614), anemia (ICD-9-CM: 280–285, A200), menorrhagia (ICD-9-CM: 626.2), female infertility (ICD-9-CM: 628, A376), and hypotension (ICD-9-CM: 458.0, 458.1, 458.9). The drugs used included progesterone, estrogen, danazol, tranexamic acid, nonsteroidal anti-inflammatory drug (NSAID) and gonadotropin releasing hormone (GnRH) agonists.

Outcome Measurement

The date of first CHM treatment after a new diagnosis of DUB was defined as the index date. We randomly matched a date between new diagnosis date of DUB and endpoint as the index date for the non-CHM cohort. Surgical events related to DUB, including hysterectomy (ICD-9-OP: 68.0, 68.3, 68.4, 68.41, 68.49, 68.5, 68.51, 68.59, 68.6, 68.7 and 69.0) and endometrial ablation (ICD-9-OP: 68.23) after the index date were measured. The outcome measurement was the comparison of incidences of surgical events in the two cohorts with the variable of comorbidities and drug used before the end of December 31, 2013.

Statistical Analyses

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, U.S.A.), and $p < 0.05$ in two-tailed tests indicate statistical significance. For each variable, we used Cox proportional hazard regression to analyze the hazard ratios (HRs) and 95% confidence interval (95% CI). The Kaplan-Meier method was used to determine the cumulative incidence of surgery in both cohorts, and the Log rank test was used to compare incidence curves between the CHM and non-CHM cohorts.

Results

We matched 4642 randomly selected patients for each group by use of 1:1 propensity score analysis for the CHM and non-CHM users. The baseline characteristics of both groups are shown in Table 1, and they were similar in age, comorbidities, and drugs used. CHM users were more dominant in the 18–39-year-old age group than the >40-year-old age group.

The most common comorbidity was inflammatory disease of the ovary (almost 20%). Nearly all patients in both cohorts used NSAIDs, and approximately 65% of CHM users took ranexamic acid. The mean duration between the initial diagnosis of DUB and the first time receiving Chinese herbal medicine was approximately 915 days (Table 1).

Table 1 Characteristics of Dysfunctional Uterine Bleeding Patients According to Use of Chinese Herb Medicine after Matching

Variable	Patients with DUB				p-value*
	Chinese Herb Medicine Used				
	Non-CHM Users (n=4642)		CHM Users (n=4642)		
	n	%	n	%	
Age Mean±SD (years)	34.51(10.21)		33.63(10.29)		<0.0001 ^a
Age Group, years					0.1656
18–39	3201	68.96	3211	69.17	
40–64	1402	30.2	1407	30.31	
Older than 65	39	0.84	24	0.52	
Comorbidities					
Inflammatory Disease of Ovary	964	20.77	902	19.43	0.1083
Anemia	449	9.67	449	9.67	0.99
Menorrhagia	285	6.14	277	5.97	0.7277
Dysmenorrhea	275	5.92	274	5.9	0.9649
Female infertility	158	3.4	144	3.1	0.4128
Hypotension	4	0.09	4	0.09	0.99 [†]

(Continued)

Table 1 (Continued).

Variable	Patients with DUB				p-value*
	Chinese Herb Medicine Used				
	Non-CHM Users (n=4642)		CHM Users (n=4642)		
	n	%	n	%	
Childbirth status					0.0396
No	2401	51.72	2500	53.86	
Yes	2241	48.28	2142	46.14	
Drug used					
NSAID	4450	95.86	4600	99.1	<0.0001
Tranexamic Acid	2550	54.93	2986	64.33	<0.0001
Progesterone	2259	48.66	2735	58.92	<0.0001
Estrogen	1992	42.91	2310	49.76	<0.0001
Danazol	37	0.8	68	1.46	0.0023
GnRH agonists	2	0.04	2	0.04	0.99 [†]
Interval Between Onset of DUB Disease and the Index Date, Days, Mean (Median)	952 (649)		915 (616)		0.0551 ^a
Follow Time (Mean, Median) (Years)	5.17 (4.57)		6.30 (5.55)		

Note: *Chi-Square Test, ^a t-test, [†]fisher exact test.

Abbreviations: DUB, dysfunctional uterine bleeding; CHM, Chinese herbal medicine; NSAID, nonsteroidal anti-inflammatory drug; GnRH, Gonadotropin Releasing Hormone.

During the follow-up period, there were 631 patients included in our study who received surgery (Table 2). A higher incidence of surgery was revealed in the 40–64-year-old group (adjusted HR 2.41). Patients with comorbidities of inflammatory disease of the ovary, anemia, menorrhagia and dysmenorrhea were more likely to receive surgery than patients without comorbidities. Patients without childbirth status were more likely to receive surgery than the childbirth

Table 2 Cox Model with Hazard Ratios and 95% Confidence Intervals of Surgery Associated with Chinese Herb Medicine and Covariates among Dysfunctional Uterine Bleeding Patients

Variable	DUB Cohort						
	Surgery no. (n=631)	Crude*			Adjusted [†]		
		HR	(95% CI)	p-value	HR	(95% CI)	p-value
CHM Use							
Non-CHM User	485	1.00	reference		1.00	reference	
CHM User	146	0.27	(0.22–0.32)	<0.0001	0.27	(0.22–0.33)	<0.0001
Age Group, Years							
18–39	275	1.00	reference		1.00	reference	
40–64	352	3.05	(2.61–3.57)	<0.0001	2.47	(2.05–2.99)	<0.0001
Older than 65	4	1.51	(0.56–4.06)	0.4114	1.09	(0.40–2.96)	0.86
Comorbidities (ref=non-)							
Inflammatory Disease of Ovary	162	1.45	(1.21–1.73)	<0.0001	1.36	(1.13–1.63)	0.0012
Anemia	134	2.70	(2.23–3.27)	<0.0001	2.01	(1.64–2.45)	<0.0001
Menorrhagia	84	2.63	(2.09–3.31)	<0.0001	1.93	(1.52–2.45)	<0.0001
Dysmenorrhea	59	1.88	(1.44–2.46)	<0.0001	1.80	(1.37–2.37)	<0.0001
Female infertility	11	0.54	(0.3–0.97)	0.0408	0.63	(0.35–1.15)	0.131
Hypotension	1	1.92	(0.27–13.66)	0.5139	0.61	(0.08–4.39)	0.6206

(Continued)

Table 2 (Continued).

Variable	DUB Cohort						
	Surgery no. (n=631)	Crude*			Adjusted†		
		HR	(95% CI)	p-value	HR	(95% CI)	p-value
Childbirth Status (ref=non-)							
No	431	1.00	reference		1.00	reference	
Yes	200	0.51	(0.43–0.60)	<0.0001	0.82	(0.68–1.01)	0.0565
Drug used (ref=non-)							
NSAID	566	0.12	(0.1–0.16)	<0.0001	0.17	(0.13–0.22)	<0.0001
Tranexamic Acid	383	0.96	(0.82–1.12)	0.5954	1.07	(0.91–1.27)	0.4063
Progesterone	300	0.71	(0.61–0.83)	<0.0001	0.90	(0.76–1.07)	0.2402
Estrogen	271	0.80	(0.68–0.94)	0.0063	0.93	(0.78–1.10)	0.4021
Danazol	16	2.04	(1.24–3.35)	0.005	2.17	(1.31–3.59)	0.0026
GnRH Agonists	0	-	-	-	-	-	-

Notes: Crude HR * represented relative hazard ratio. Adjusted HR† represented adjusted hazard ratio: mutually adjusted for CHM use, age, comorbidities, childbirth status and drug used in Cox proportional hazard regression.

Abbreviations: DUB, dysfunctional uterine bleeding; CHM, Chinese herbal medicine; NSAID, Nonsteroidal Anti-Inflammatory Drug; GnRH, Gonadotropin Releasing Hormone.

group. Overall, the incidence of surgery was significantly lower in the CHM cohort than in the non-CHM cohort (adjusted HR 0.27, 95% CI 0.22–0.33).

The difference in the cumulative incidence of surgery between the two groups was illustrated through a Kaplan–Meier analysis (Figure 2). The cumulative incidence of surgery was significantly lower in the CHM cohort than the non-CHM cohort group during the follow-up period (Log rank test, $p < 0.001$). A total of 146 patients in the CHM cohort (4.99 per 1000 person-years) and 485 patients in the non-CHM cohort (20.19 per 1000 person-years) received surgery (adjusted HR 0.27, 95% CI 0.22–0.33) (Table 3). The incidence rates of surgery in the 18–39-year-old group and the 40–64-year-old

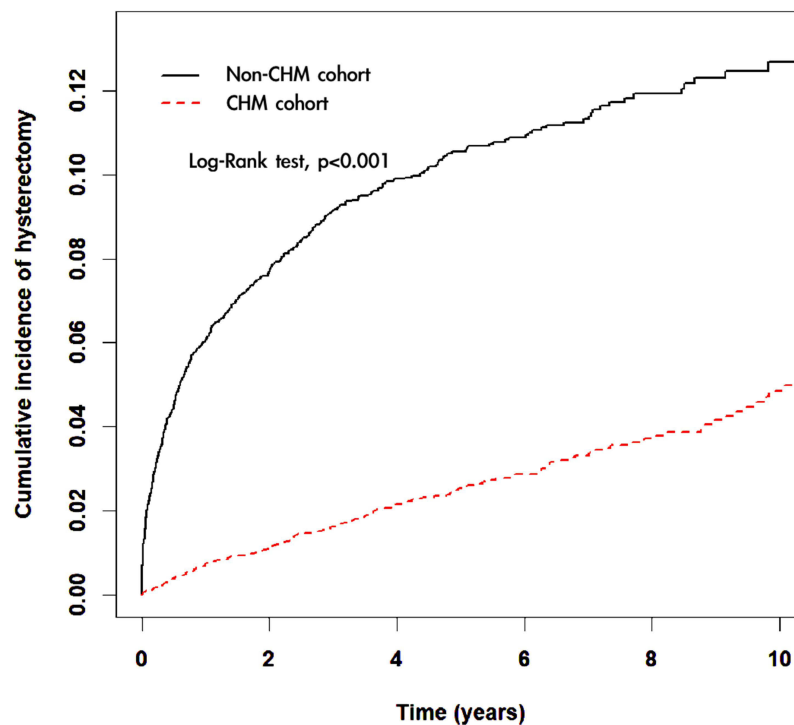


Figure 2 Cumulative incidence of surgery between the CHM cohort and non-CHM cohort. The cumulative incidence of surgeries related to dysfunctional uterine bleeding (DUB) in the CHM cohort (dashed line) is significantly lower than in the non-CHM cohort (solid line) (Log rank test, $p < 0.001$).

Table 3 Incidence Rates, Hazard Ratio and Confidence Intervals of Surgery for Dysfunctional Uterine Bleeding Patients with and without Chinese Herbal Medicine Treatment Stratified by Age, Comorbidities, Drug Used and Childbirth Status

Variables	Chinese Herb Medicine Used						Compared with non-CHM User	
	Non-CHM users (n=4642)			CHM users (n=4642)			Crude HR	Adjusted HR
	Event	Person Years	IR [†]	Event	Person Years	IR [†]	(95% CI)	(95% CI)
Total	485	24,017	20.19	146	29,264	4.99	0.27(0.22–0.32)***	0.27(0.22–0.33)***
Age Group								
18–39	207	17,233	12.01	68	20,230	3.36	0.29(0.22–0.38)***	0.29(0.22–0.39)***
40–64	274	6603	41.5	78	8832	8.83	0.25(0.19–0.32)***	0.25(0.2–0.33)***
Older than 65	4	181	22.13	0	203	0	-	-
Co-Morbidities								
No	251	16,365	15.34	77	20,046	3.84	0.27(0.21–0.34)***	0.29(0.22–0.37)***
Yes	234	7652	30.58	69	9218	7.49	0.27(0.21–0.35)***	0.26(0.2–0.34)***
Drug Used								
No	40	165	243.09	3	71	42.23	0.22(0.07–0.72)*	0.17(0.05–0.68)*
Yes	445	23,852	18.66	143	29,193	4.9	0.28(0.23–0.34)***	0.27(0.22–0.33)***
Childbirth Status								
No	340	11,898	28.58	91	15,664	5.81	0.22(0.18–0.28)***	0.23(0.18–0.29)***
Yes	145	12,119	11.96	55	13,600	4.04	0.35(0.26–0.48)***	0.37(0.27–0.51)***

Notes: Adjusted HR[†] represented adjusted hazard ratio: mutually adjusted for CHM use, age, comorbidities, childbirth status and drug used in Cox proportional hazard regression. *;<0.05; *** p<0.001. Comorbidities and drug used list as listed in the methods section.

Abbreviations: IR, incidence rates, per 1,000 person-years; CHM, Chinese herb medicine; HR, hazard ratio; CI, confidence interval.

group that used CHM were 3.36 and 8.83 per 1000 person years, respectively, which were lower than those in the comparison cohort (12.01 and 41.5 per 1000 person-years, respectively). In addition, the 18–39-year-old group and the 40–64-year-old group showed a 0.29-fold (95% CI: 0.22–0.39) and a 0.25-fold (95% CI: 0.2–0.33) lower risk of surgery, respectively, than the non-CHM cohort. CHM significantly decreased the risk of surgery in both the 18–39-year-old and the 40–64-year-old age groups. CHM also reduced the risk of surgery in DUB patients with or without comorbidities. Regardless of childbirth status or whether patients took NSAIDs, tranexamic acid or progesterone, fewer patients in the CHM cohort underwent surgery than in the non-CHM cohort.

In Tables 4 and 5, the most commonly prescribed single herbs and multi-herbal products (formulas) for the treatment of patients with DUB are listed. Yi-Mu-Cao (Herba Leonuri; *Leonurus heterophyllus* Sweet) and Jia-Wei-Xiao-Yao-San (Bupleurum and Peony Formula) was the most commonly used single herb and formula, respectively.

Table 4 The Most Commonly Prescribed Single Herbs for the Treatment of Dysfunctional Uterine Bleeding

Pin-Yin Name	Chinese Materia Medica name	Botanical Name	Indication for TCM syndrome
Yi-Mu-Cao	Herba Leonuri	<i>Leonurus heterophyllus</i> Sweet	Menstrual irregularities due to blood stasis with edema
Xiang-Fu	Rhizoma Cyperi	<i>Cyperus rotundus</i> L.	Irregular menstruation because of liver qi stagnation
Dan-Shen	Radix Salviae Miltiorrhizae	<i>Salvia miltiorrhiza</i> Bge.	Irregular menstruation because of blood and qi stagnation
Yan-Hu-Suo	Rhizoma Corydalidis	<i>Corydalis yanhusuo</i> W. T. Wang	Irregular menstruation because of liver qi stagnation
Xu-Duan	Radix Dipsaci	<i>Dipsacus asperoides</i> , C. Y.Chent et TM Ai	Deficiency in liver and kidney
Xian-He-Cao	Herba Agrimoniae	<i>Agrimonia eupatoria</i> L. var. <i>pilosa</i> Mak	Excessive bleeding
Han-Lian-Cao	Herba eclipatae	<i>Eclipta prostrata</i> Linn, <i>Eclipta alba</i> (L.) Hassk.	Yin deficiency in liver and kidney; excessive bleeding during menopause
Tu-Si-Zi	Semen Cuscutae Chinensis	<i>Cuscuta chinensis</i> Lam.	Yin deficiency in liver and kidney; infertility
Du-Zhong	Cortex Eucommiae Ulmoidis	<i>Eucommia ulmoides</i> Oliv.	Deficiency in liver and kidney
Nu-Zhen-Zi	Fructus Ligustri Lucidi	<i>Ligustrum lucidum</i>	Yin deficiency in liver and kidney

Abbreviation: TCM, Traditional Chinese medicine.

Table 5 The Most Commonly Prescribed Chinese Herbal Formulas for the Treatment of Dysfunctional Uterine Bleeding

Pin-Yin Name	English Name	Constitutions			TCM Indication
		Pin-Yin Name	Chinese Materia Medica name	Botanical Name	
Jia-Wei-Xiao-Yao-San	Bupleurum and Peony Formula	Dang-Gui	Radix Angelicae Sinensis	<i>Angelica sinensis</i> (Oliv.) Diels	Irregular menstruation because of spleen qi deficiency and liver blood deficiency with heat; liver qi stagnation
		Fu-Ling	Poria,	<i>Poria cocos</i> (Schw.) Wolf	
		Zhi-Zi	Fructus Gardeniae	<i>Gardenia jasminoides</i> J.Ellis	
		Bo-He	Herba Menthae Haplocalycis	<i>Mentha haplocalyx</i> Briq.Field	
		Bai-Shao	Radix Paeoniae Alba	<i>Paeonia lactiflora</i> Pall	
		Chai-Hu	Radix Bupleuri	<i>Bupleurum chinense</i> DC.	
		Gan-Cao	Radix Glycyrrhizae	<i>Glycyrrhiza uralensis</i> Fisch	
		Bai-Zhu	Rhizoma Atractylodis Macrocephalae	<i>Atractylis macrocephala</i> Koidz	
		Mu-Dan-Pi	Cortex Moutan Radicis	<i>Paeonia suffruticosa</i> Andr.	
		Wei-Jiang	Rhizoma Zingiberis officinales	<i>Zingiber officinale</i> Rosc.	
Gui-Zhi- Fu-Ling-Wan	Cinnamon and Poria Pills	Gui-Zhi	Ramulus Cinnamomi Cassiae	<i>Cinnamomum cassia</i> Blume	Blood stasis in pelvic cavity
		Fu-Ling	Poria	<i>Poria cocos</i> (Schw.) Wolf	
		Mu-Dan-Pi	Cortex Moutan Radicis	<i>Paeonia suffruticosa</i> Andr.	
		Chi-Shao	Radix Paeoniae Lactiflorae	<i>Paeonia lactiflora</i> Pall.	
		Tao-Ren	Semen Persicae	<i>Prunus persica</i> (L.) Batsch.	
Dang-Gui-Shao-Yao-San	Tangkuei and Peony Powder	Dang-Gui	Radix Angelicae Sinensis	<i>Angelica sinensis</i> (Oliv.) Diels	Liver blood deficiency
		Fu-Ling	Poria	<i>Poria cocos</i> (Schw.) Wolf	
		Bai-Shao	Radix Paeoniae Alba	<i>Paeonia lactiflora</i> Pall.	
		Bai-Zhu	Rhizoma Atractylodis Macrocephalae	<i>Atractylodes macrocephala</i> Koidz	
		Chuan-Xiong	Rhizoma Chuanxiong	<i>Ligusticum chuanxiong</i> Hort.	
		Ze-Xie	Rhizoma Alismatis	<i>Alisma plantago-aquatica</i> L.	

Table 5 (Continued).

Pin-Yin Name	English Name	Constitutions			TCM Indication
		Pin-Yin Name	Chinese Materia Medica name	Botanical Name	
Gui-Pi-Tang	Restore the Spleen Decoction	Ren-Shen Long-Yan-Rou Huang-Qi Gan-Cao Bai-Zhu Fu-Ling Mu-Xiang Dang-Gui Suan-Zao-Ran Yuan-Zhi Sheng-Jiang Da-Zao	Radix Ginseng Arillus Euphoriae Longanae Radix Astragali Radix Glycyrrhizae Rhizoma Atractylodis Macrocephalae Poria Radix Aucklandiae Radix Angelicae Sinensis Semen Zizyphi Spinosae Radix Polygalae Tenuifoliae Radix Zingiberis officinalis Fructus Zizyphi Jujube	<i>Panax ginseng</i> C. A. Mey <i>Dimocarpus longan</i> Lour. <i>Astragalus henryi</i> Oliv. <i>Glycyrrhiza uralensis</i> Fisch <i>Atractylis macrocephala</i> Koidz <i>Poria cocos</i> (Schw.) Wolf <i>Aucklandia lappa</i> Deene <i>Angelica sinensis</i> (Oliv.) Diels <i>Ziziphus jujube</i> var. <i>Spinosa</i> (Bunge) Hu ex H. F. Chou <i>Polygala tenuifolia</i> Willd. <i>Zingiber officinale</i> Rosc. <i>Ziziphus jujube</i> Mill. Var. <i>inermis</i> Bge.	Blood deficiency; vaginal spotting because of qi deficiency
Shao-Fu-Zhu-Yu-Tang	Drive Out Stasis from the Lower Abdomen Decoction	Xiao-Hui-Xiang Pao-Jiang Yan-Hu-Suo Dang-Gui Chuan-Xiong Mo-Yao Rou-Gui Chi-Shao Pu-Huang Wu-Ling-Zhi	Fructus Foeniculi Vulgaris Rhizoma Zingiberis officinales Rhizoma Corydalis Radix Angelicae Sinensis Rhizoma Chuanxiong Myrrh Ramulus Cinnamomi Cassiae Radix Paeoniae Lactiflorae Pollen Typhae Excrementum Troglodyteri Xanthipes	<i>Foeniculum vulgare</i> Mill. <i>Zingiber officinale</i> Rosc. <i>Corydalis yanhusuo</i> W. T. Wang <i>Angelica sinensis</i> (Oliv.) Diels <i>Ligusticum chuanxiong</i> Hort. <i>Commiphora molmol</i> Engl. <i>Cinnamomum cassia</i> Blume <i>Paeonia lactiflora</i> Pall. <i>Typha angustifolia</i> L. <i>Troglodytes xanthipes</i> Milne-Edwards	Blood stasis and qi stagnation
Tao-He-Cheng-Qi-Tang	Kernel Qi-Coordinating Decoction	Tao-Ren, Gui-Zhi Da-huang Mang-Xiao Zhi-Gan-Cao	Semen Persicae Ramulus Cinnamomi Cassiae Radix et Rhizoma Rhei Natrii Sulfas, Radix Glycyrrhizae	<i>Prunus persica</i> (L.) Batsch <i>Cinnamomum cassia</i> Blume <i>Rheum palmatum</i> L. Mirabilitum <i>Glycyrrhiza uralensis</i> Fisch	Accumulation of blood stasis and heat in the lower burner

Xiao-Yao-San	Free Wanderer Powder	Dang-Gui Fu-Ling Bo-He Bai-Shao Chai-Hu Gan-Cao Bai-Zhu Wei-Jiang	Radix Angelicae Sinensis Poria Herba Menthae Haplocalycis Radix Paeoniae Alba Radix Bupleuri Radix Glycyrrhizae Rhizoma Atractylodis Macrocephalae Rhizoma Zingiberis officinales Semen Persicae Flos Carthami Tinctorii Radix Rehmanniae Radix Paeoniae Lactiflorae Radix Angelicae Sinensis Radix Ligustici Radix Achyranthis Bidentatae Radix Bupleuri, Radix Platycodonis Fructus CitriAurantii Radix Glycyrrhizae	<i>Angelica sinensis</i> (Oliv.) Diels <i>Poria cocos</i> (Schw.) Wolf <i>Mentha haplocalyx</i> Briq.Field <i>Paeonia lactiflora</i> Pall <i>Bupleurum chinense</i> DC. <i>Glycyrrhiza uralensis</i> Fisch <i>Atractylis macrocephala</i> Koidz <i>Zingiber officinale</i> Rosc. <i>Prunus persica</i> (L.) Batsch <i>Carthamus tinctorius</i> L. <i>Rehmannia glutinosa</i> Libosch <i>Paeonia lactiflora</i> Pall <i>Angelica sinensis</i> (Oliv.) Diels <i>Ligusticum chuanxiong</i> Hort. <i>Achyranthes bidentata</i> Bl. <i>Bupleurum chinense</i> DC. <i>Platycodon grandiflorus</i> (Jacq.) A.DC. <i>Citrus aurantium</i> L. <i>Glycyrrhi za uralensis</i> Fisch	Liver qi constraint with deficiency of the spleen Blood stasis in the “mansion of blood”
Xue-Fu-Zhu-Yu-Tang	House of Blood Stasis-Expelling Decoction	Tao-Ren Hong-Hua Shu- Di-Huang Chi-Shao Dang-Gui Chuan-Xiong Niu-Xi Chai-Hu Jie- Geng Zhi-Ke Gan-Cao			

Abbreviation: TCM, Traditional Chinese medicine.

Discussion

Our study was the first nationwide population-based study investigating on the association of CHM with the need for surgeries (hysterectomy and endometrial ablation) in DUB patients. The results of our study demonstrated that integrative CHM treatment may be beneficial for patients with DUB. It is associated with a decreased incidence of surgery compared to the non-CHM group. The cumulative incidence rate of surgery in patients with DUB was significantly lower in CHM users in comparison with non-CHM users during the follow-up period. CHM users displayed an average 73% decreased risk of surgical events compared with non-CHM users (0.27, 95% CI 0.22–0.33, $p < 0.001$).

Patients in the 40–64-year-old age group had a higher incidence rate of surgery. This is consistent with a previous study that showed that patients >40 years old have a higher incidence of dysfunctional uterine bleeding. Moreover, patients in that age group most likely no longer have plans for child-bearing. Our study revealed that younger patients preferred to receive CHM treatment, which was consistent with previous studies.^{11,15,18,19}

Patients who were taking danazol simultaneously were more likely to undergo surgery (adjusted HR 2.19, 95% CI 1.32–3.63), and patients who used NSAIDs were less likely to receive surgery (adjusted HR 0.17, 95% CI 0.13–0.22, $p < 0.001$). Patients who took NSAIDs simultaneously tended to have better pain and bleeding control,²⁰ so the incidence of surgery was significantly reduced. Patients who used danazol were likely to have more complicated circumstances,²¹ so the incidence of surgery was much higher. Patients with comorbidities of anemia, menorrhagia, dysmenorrhea and inflammatory disease of the ovary were more likely to have undergone hysterectomy or endometrial ablation.

Patients with the comorbidities of dysmenorrhea and inflammatory disease of the ovary had pathological effects that were similar to those of DUB; these effects may have been caused by the dysregulated endometrial vascular development²² and the imbalance of prostaglandins between the vasoconstriction effect and vasodilation of PGF_{2a}, PGE₂ and PGI₂, which is the possible mechanism of DUB.^{23–25} This is consistent with a previous study that found that dysmenorrhea may increase the risk of needing hysterectomy after endometrial ablation.²⁶ Pain or dysmenorrhea may be an important factor in the selection of DUB treatment.^{27,28} Our study also revealed that patients with NSAID use had a lower incidence of surgery. The comorbidities of menorrhagia and associated anemia were consistent with the surgical treatment guidelines of DUB, which state that Hb < 10 can increase the need for surgery.²⁹

The main disadvantage of medical treatment options is the potential recurrence of symptoms. Complications and long-term post-operation problems following hysterectomy cannot be ignored despite the fact that hysterectomy will immediately stop heavy menstrual bleeding. Hysterectomy impairs patients' ovarian function and may cause early menopause, which in turn increases the risk for cardiovascular diseases.³⁰ Some studies have revealed an association between hysterectomy and high blood pressure, and an abnormal lipid profile.^{31,32} Therefore, many women would likely benefit from trying TCM for help.

We previously identified the prescription pattern of the CHM for patients with DUB.¹¹ From the perspective of TCM theory, these herbs can be categorized according to the TCM syndrome differentiation. Among the top 10 commonly prescribed single herbs and herbal formulas, some of them are used for relieving blood stasis and qi stagnation and thus might relieve pain, while some are used to nurture Yin and blood to restore the uterine function according to the TCM theory (Table 4 and Table 5). It is necessary to clarify that these herbal prescriptions should be based on TCM diagnosis. The application of herbs may be individualized and thus the prescriptions may be different between patients.

Yi-Mu-Cao (Herba Leonuri), Xiang-Fu (Rhizoma Cyperi) and Yan-Hu-Suo (Rhizoma Corydalis) were the mostly commonly used single herbs for patients with DUB. A couple experimental models may explain the potential mechanisms of these single herbs. Yi-Mu-Cao has been traditionally used to help activate blood and resolve stasis. Leonurine, an alkaloid present in Yi-Mu-Cao, has anti-fibrotic, antioxidant, anti-inflammatory and analgesic effects.³³ It can also induce and strengthen uterine contractions, so it is used in the treatment of menstrual disorders.³⁴ Additionally, Xiang-Fu (Rhizoma Cyperi) has been used as an estrogenic agent in estrogen-deprived mice.³⁵ The component tetrahydropalmatine from Yan-Hu-Suo was revealed to inhibit D₂ dopamine receptors and have analgesic effects.³⁶

Our previous study also identified that Jia-Wei-Xiao-Yao-San, Dang-Gui-Shao-Yao-San and Gui-Zhi-Fu-Ling-Wan were commonly used for patients with DUB.¹¹ Jia-Wei-Xiao-Yao-San has been widely used to treat menstrual disorders and the emotional and psychological symptoms. It was reported that its anti-depressant effect might be related to regulation of TNF- α levels.³⁷ The pharmacological properties of Gui-Zhi-Fu-Ling-Wan have been reported to inhibit the cascade of the overproduction of COX-2 and iNOS.³⁸ It also significantly suppresses the protein and mRNA levels of

MIF, IL-6, IL-8, and TNF- α .³⁹ It has been demonstrated to have protective effects against vascular injury and to inhibit the proliferation of uterine leiomyoma cells.^{40,41} Dang-Gui-Shao-Yao-San significantly suppress oxytocin-evoked PGF2 α production of rat endometrial epithelial cells and has antagonistic action on uterine contraction.^{42,43}

Clinically, the current treatment options for AUB can be medical, surgical, or a combination of both, depending on the underlying cause. It is also necessary to consider key factors such as the patient's age, fertility desire, symptom relief, and co-morbidities.⁴⁴ Medical treatments typically involve iron supplementation and the use of hormonal or non-hormonal therapies. Surgical options include the removal of focal lesions, endometrial resection or destruction, and hysterectomy.⁴⁵ According to our study, CHM should be integrated as a kind of medical treatment for the preservation of fertility function, restoration of regular menstrual period, relieving symptoms and improving quality of life. The treatment should also be tailored according to the needs of the patients. For example, those who are at a child-bearing age should consider CHM treatment before undergoing surgery.

There were some limitations to our research; for instance, the results of the laboratory data and the image examinations were not available in the database. Consequently, the disease severity between the TCM seekers and the non-TCM seekers could not be evaluated in this study. Thus, we tried to exclude those who were diagnosed as having cervical cancer, endometrial cancer, or ovarian cancer from our study population. We also used a propensity score to match the CHM and non-CHM cohorts. On the other hand, levonorgestrel intrauterine devices were not reimbursed by the NHI program until 2015, so we could not identify subjects who had used this device. Even though, our findings support the idea to conduct a high-quality randomized controlled trial to evaluate the efficacy and safety of Chinese herbal medicine.

Conclusions

This is the first large-scale population-based study on the surgery rate of TCM users among DUB patients. We found that complementary CHM is associated with a reduced surgical rate for DUB patients regardless of age, childbirth status, comorbidities, or drug use. Clinically, CHM should be integrated as a kind of medical treatment for the preservation of fertility function, restoration of regular menstrual period, relieving symptoms and improving quality of life. A high-quality randomized controlled clinical trial to determine the efficacy of CHM for DUB patients should be conducted in the future.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taiwan (CMUH104-REC2-115(CR-4)). The patient consent was exempted for the total anonymity of all research data in this study.

Acknowledgments

We are grateful to Health Data Science Center, China Medical University Hospital for providing administrative, technical and funding support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was financially supported by the "Chinese Medicine Research Center, China Medical University" from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (CMRC-CHM-1). This study was also supported in part by China Medical University Hospital, Taiwan (DMR-110-2). This study is also supported in part by Taiwan Ministry of Health and Welfare Clinical

Trial Center (MOHW111-TDU-B-212-134004), China Medical University Hospital. The funders had no role in the study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

Disclosure

The authors declare that they have no conflicts of interest in this work.

References

- Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. *Value Health*. 2007;10(3):183–194. doi:10.1111/j.1524-4733.2007.00168.x
- Penninx JP, Mol BW, Engels R, et al. Bipolar radiofrequency endometrial ablation compared with hydrothermablation for dysfunctional uterine bleeding: a randomized controlled trial. *Obstetrics Gynecol*. 2010;116(4):819–826. doi:10.1097/AOG.0b013e3181f2e3e3
- Frick KD, Clark MA, Steinwachs DM, et al. Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. *Women's Health Issues*. 2009;19(1):70–78. doi:10.1016/j.whi.2008.07.002
- American College of O. Gynecologists: ACOG committee opinion no. 557: management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obstetrics Gynecol*. 2013;121(4):891–896. doi:10.1097/01.AOG.0000428646.67925.9a
- Matteson KA, Rahn DD, Wheeler TL 2nd, et al. Society of gynecologic surgeons systematic review g: nonsurgical management of heavy menstrual bleeding: a systematic review. *Obstetrics Gynecol*. 2013;121(3):632–643. doi:10.1097/AOG.0b013e3182839e0e
- Solnik MJ, Munro MG. Indications and alternatives to hysterectomy. *Clin Obstet Gynecol*. 2014;57(1):14–42. doi:10.1097/GRF.0000000000000010
- Spencer JC, Louie M, Moulder JK, et al. Cost-effectiveness of treatments for heavy menstrual bleeding. *Am J Clin Exp Obstet Gynecol*. 2017;217(5):e571–574e579. doi:10.1016/j.ajog.2017.07.024
- Spilsbury K, Hammond I, Bulsara M, Semmens JB. Morbidity outcomes of 78,577 hysterectomies for benign reasons over 23 years. *BJOG: Int J Obstet Gynaecol*. 2008;115(12):1473–1483. doi:10.1111/j.1471-0528.2008.01921.x
- Clayton RD. Hysterectomy. *Best Pract Res Clin Obstet Gynaecol*. 2006;20(1):73–87. doi:10.1016/j.bpobgyn.2005.09.007
- Davies A, Magos AL. 4 Indications and alternatives to hysterectomy. *Baillière's Clin Obstet Gynaecol*. 1997;11(1):61–75.
- Lin YR, Wu MY, Chiang JH, Yen HR, Yang ST. The utilization of traditional Chinese medicine in patients with dysfunctional uterine bleeding in Taiwan: a nationwide population-based study. *BMC Complement Alter Med*. 2017;17(1):427. doi:10.1186/s12906-017-1939-1
- Chao J, Ko CY, Lin CY, et al. Ethnobotanical survey of natural galactagogues prescribed in traditional Chinese medicine pharmacies in Taiwan. *Front Pharmacol*. 2020;11:625869.
- Chao SL, Huang LW, Yen HR. Pregnancy in premature ovarian failure after therapy using Chinese herbal medicine. *Chang Gung Med J*. 2003;26(6):449–452.
- Wang C, Lin KY, Wu MY, et al. Adjunctive Chinese herbal medicine treatment is associated with an improved survival rate in patients with cervical cancer in Taiwan: a matched cohort study. *Integr Cancer Ther*. 2021;20:15347354211061752. doi:10.1177/15347354211061752
- Yen HR, Chen YY, Huang TP, et al. Prescription patterns of Chinese herbal products for patients with uterine fibroid in Taiwan: a nationwide population-based study. *J Ethnopharmacol*. 2015;171:223–230. doi:10.1016/j.jep.2015.05.038
- Yen HR, Huang TP, Sun MF. Chinese medicine usage in Taiwan: a nationwide population-based study. *RCHM J*. 2013;10(2):21–27.
- Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). *Epidemiol Health*. 2018;40:e2018062.
- Pan JC, Tsai YT, Lai JN, Fang RC, Yeh CH. The traditional Chinese medicine prescription pattern of patients with primary dysmenorrhea in Taiwan: a large-scale cross sectional survey. *J Ethnopharmacol*. 2014;152(2):314–319. doi:10.1016/j.jep.2014.01.002
- Shih CC, Liao CC, Su YC, Tsai CC, Lin JG. Gender differences in traditional Chinese medicine use among adults in Taiwan. *PLoS One*. 2012;7(4):e32540. doi:10.1371/journal.pone.0032540
- Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*. 2015;2015(7):CD001751. doi:10.1002/14651858.CD001751.pub3
- Pontis A, D'Alterio MN, Pirarba S, de Angelis C, Tinelli R, Angioni S. Adenomyosis: a systematic review of medical treatment. *J Gynecol Endocrinol*. 2016;32(9):696–700. doi:10.1080/09513590.2016.1197200
- Biswas Shivhare S, Bulmer JN, Innes BA, Hapangama DK, Lash GE. Altered vascular smooth muscle cell differentiation in the endometrial vasculature in menorrhagia. *Hum Reprod*. 2014;29(9):1884–1894. doi:10.1093/humrep/deu164
- Critchley HO, Maybin JA. Molecular and cellular causes of abnormal uterine bleeding of endometrial origin. *Semin Reprod Med*. 2011;29(5):400–409. doi:10.1055/s-0031-1287664
- Aguilar HN, Mitchell BF. Physiological pathways and molecular mechanisms regulating uterine contractility. *Hum Reprod Update*. 2010;16(6):725–744. doi:10.1093/humupd/dmq016
- Hapangama DK, Bulmer JN. Pathophysiology of heavy menstrual bleeding. *Women's Health*. 2016;12(1):3–13. doi:10.2217/whe.15.81
- Billow MR, El-Nashar SA. Management of abnormal uterine bleeding with emphasis on alternatives to hysterectomy. *Obstet Gynecol Clin North America*. 2016;43(3):415–430. doi:10.1016/j.ogc.2016.04.002
- Wheeler TL 2nd, Murphy M, Rogers RG, et al. Society of gynecologic surgeons systematic review g: clinical practice guideline for abnormal uterine bleeding: hysterectomy versus alternative therapy. *J Minim Invasive Gynecol*. 2012;19(1):81–88. doi:10.1016/j.jmig.2011.10.001
- Su SY, Muo CH, Sung FC, Morisky DE. Reduction of surgery rate in endometriosis patients who take Chinese medicine: a population-based retrospective cohort study. *Complement Ther Med*. 2014;22(4):632–639. doi:10.1016/j.ctim.2014.06.010
- Schilling J, Wyss P, Faisst K, Gutzwiller F, Haller U. Swiss consensus guidelines for hysterectomy. *Int J Gynecol Obstet*. 1999;64(3):297–305. doi:10.1016/S0020-7292(98)00246-X
- Heliövaara-Peippo S, Oksjoki R, Halmesmaki K, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on cardiovascular disease risk factors in menorrhagia patients: a 10-year follow-up of a randomised trial. *Maturitas*. 2011;69(4):354–358. doi:10.1016/j.maturitas.2011.05.004

31. Zhang Y, Lee ET, Cowan LD, North KE, Wild RA, Howard BV. Hysterectomy prevalence and cardiovascular disease risk factors in American Indian women. *Maturitas*. 2005;52(3–4):328–336. doi:10.1016/j.maturitas.2005.05.009
32. Howard BV, Kuller L, Langer R, et al. Risk of cardiovascular disease by hysterectomy status, with and without oophorectomy: the Women's health initiative observational study. *Circulation*. 2005;111(12):1462–1470. doi:10.1161/01.CIR.0000159344.21672.FD
33. Cheng H, Bo Y, Shen W, et al. Leonurine ameliorates kidney fibrosis via suppressing TGF-beta and NF-kappaB signaling pathway in UUO mice. *Int Immunopharmacol*. 2015;25(2):406–415. doi:10.1016/j.intimp.2015.02.023
34. Fan J, Wei F, Zhang Y, et al. Combining Sprague-Dawley rat uterus cell membrane chromatography with HPLC/MS to screen active components from Leonurus artemisia. *Pharm Biol*. 2016;54(2):279–284. doi:10.3109/13880209.2015.1033562
35. Kim HG, Hong J, Huh Y, et al. Cyperi Rhizoma inhibits the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced reduction in nigrostriatal dopaminergic neurons in estrogen-deprived mice. *J Ethnopharmacol*. 2013;148(1):322–328. doi:10.1016/j.jep.2013.04.038
36. Chu H, Jin G, Friedman E, Zhen X. Recent development in studies of tetrahydroprotoberberines: mechanism in antinociception and drug addiction. *Cell Mol Neurobiol*. 2008;28(4):491–499. doi:10.1007/s10571-007-9179-4
37. Ushiroyama T, Ikeda A, Sakuma K, Ueki M. Changes in serum tumor necrosis factor (TNF-alpha) with kami-shoyo-san administration in depressed climacteric patients. *Am J Chin Med*. 2004;32(4):621–629. doi:10.1142/S0192415X04002259
38. Yoshihisa Y, Furuichi M, Ur Rehman M, Ueda C, Makino T, Shimizu T. The traditional Japanese formula keishibukuryogan inhibits the production of inflammatory cytokines by dermal endothelial cells. *Mediators Inflamm*. 2010;2010:804298. doi:10.1155/2010/804298
39. Sun L, Liu L, Zong S, et al. Traditional Chinese medicine guizhi fuling capsule used for therapy of dysmenorrhea via attenuating uterus contraction. *J Ethnopharmacol*. 2016;191:273–279. doi:10.1016/j.jep.2016.06.042
40. Goto H, Shimada Y, Sekiya N, et al. Effects of Keishi-bukuryo-gan on vascular function and hemorheological factors in spontaneously diabetic (WBN/kob) rats. *Phytomedicine: Int J Phytotherapy and Phytopharmacology*. 2004;11(2–3):188–195. doi:10.1078/0944-7113-00336
41. Shen Q, Ye W, Hu X, Zhao C, Zhou L, Zhu X. The effects of guizhi fuling capsule drug serum on uterine leiomyoma cells and its mechanism. *eCAM*. 2016;2016:2393640. doi:10.1155/2016/2393640
42. Hua YQ, Su SL, Duan JA, Wang QJ, Lu Y, Chen L. Danggui-shaoyao-San, a traditional Chinese prescription, suppresses PGF2alpha production in endometrial epithelial cells by inhibiting COX-2 expression and activity. *Phytomedicine: Int J Phytotherapy and Phytopharmacology*. 2008;15(12):1046–1052. doi:10.1016/j.phymed.2008.06.010
43. Hsu CS, Yang JK, Yang LL. Effect of "Dang-Qui-Shao-Yao-San" a Chinese medicinal prescription for dysmenorrhea on uterus contractility in vitro. *Phytomedicine: Int J Phytotherapy and Phytopharmacology*. 2006;13(1–2):94–100. doi:10.1016/j.phymed.2004.06.016
44. Whitaker L, Critchley HO. Abnormal uterine bleeding. *Best Pract Res Clin Obstet Gynaecol*. 2016;34:54–65. doi:10.1016/j.bpobgyn.2015.11.012
45. Levy-Zauberman Y, Pourcelot AG, Capmas P, Fernandez H. Update on the management of abnormal uterine bleeding. *J Gynecol Obstet Hum Reprod*. 2017;46(8):613–622. doi:10.1016/j.jogoh.2017.07.005