

CLINICAL RESEARCH

Medication Rules of Traditional Chinese Medicine for Treating Threatened Abortion in the Early Stage of Pregnancy with Subchorionic Haematoma Based on Data Mining

ZENG Li (曾 丽)¹, ZU Li (祖 丽)¹, CHEN Li (陈 莉)¹, WANG Feng-yi (王峰义)², LI Li (李 莉)³

1. The Seventh Clinical Medical College of Guangzhou University of Chinese Medicine, Shenzhen 518133, China

2. Acupuncture and Rehabilitation College, Guangzhou University of Chinese Medicine, Guangzhou 510405, China

3. The First Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou 510405, China

Correspondence to: LI Li, Email: 1776782731@qq.com

Supported by: Clinical observation and metabolomics study of patients with Phlegm-stasis interjunction polycystic ovary syndrome by Guangdong Bureau of Traditional Chinese Medicine (20202066), Shenzhen Baoan district science and technology plan (20200505115910988); Observation on the efficacy of Jiaxiao Dingjing Decoction combined with clomiphene in the treatment of polycystic ovary syndrome (2020JD526)

ABSTRACT **Objective:** Using data mining technology to explore the rules of traditional Chinese medicine (TCM) in the treatment of threatened abortion in the early stage of pregnancy with sub-chorionic haematoma (SCH). **Methods:** Literature of TCM in the treatment of threatened abortion in the early stage of pregnancy with SCH were retrieved from CNKI, VIP, WANFANG and Pubmed, EMBASE. The literature information database was established to be used for descriptive analysis, association rule analysis and cluster analysis of relevant data. **Results:** A total of 100 literatures were included, involving 114 Chinese herbs. The efficacy of Chinese herbs were mainly tonic drugs, hemostatic drugs, heat-clearing drugs, dissolving blood stasis and hemostatic drugs. The medicinal properties were mostly mild and warm, and the taste of the drug was mainly sweet, bitter and pungent. The liver meridian, spleen meridian and kidney meridian were frequently used. The commonly used drug pair combination was "Xu duan (*Radix dipsaci*, 续断)-Tusizi (*Semen Cuscutae*, 菟丝子)", and the core combination was "Tusizi-Xu duan-Ejiao (*Donkey-hide gelatin*, 阿胶)-Baizhu (*Atractylodes macrocephala*, 白术)-Dangshen (*Codonopsis pilosula*, 党参)". Commonly used drugs for removing blood stasis and hemostasis were with Sanqi (*Panax notoginseng*, 三七), Puhuang (*cattail pollen*, 蒲黄), and Qiancao (*Radix Rubiae*, 茜草). **Conclusion:** Data mining traditional Chinese medicine for the treatment of threatened abortion in the early stage of pregnancy with SCH clinically commonly used drug efficacy, taste, meridian, commonly used drug pairs, core combination and commonly used blood stasis hemostatic drugs, has important reference significance for the treatment of threatened abortion in the early stage of pregnancy combined with SCH.

KEYWORDS Threatened abortion for early stage of pregnancy; Sub-chorionic haematoma; Data mining; Medication rules; Removing blood stasis and stopping bleeding; TCM

INTRODUCTION

Spontaneous abortion is a common disease in obstetrics and gynecology, of which more than 80% are early abortion.^[1] The incidence of subchorionic haematoma (SCH) is high in early pregnancy,^[2] and its occurrence increases the spontaneous abortion rate.^[3] The spontaneous abortion rate of severe SCH is as high as 55.6%.^[4,5] SCH refers to the separation

and bleeding of the chorionic membrane from the membrane, resulting in blood gathering between the chorionic membrane and the decidual membrane to form hematoma. SCH refers to the formation of hematoma between the chorionic membrane and decidual membrane, which is an important risk factor for early abortion. Therefore, safe and effective treatment of early threatened abortion combined with SCH is of great value. At present, progesterone

is often used in modern medicine to treat early threatened abortion combined with SCH, and the effect is still to be discussed. Therefore, it is of great significance to explore safe and effective treatment for early threatened abortion complicated with SCH. Early threatened abortion combined with SCH belongs to the category of fetal leakage and fetal disturbance in traditional Chinese medicine (TCM). Relevant studies have proved the effectiveness of TCM, but there is no relevant law analysis to guide clinical diagnosis and treatment. This paper comprehensively and systematically summarized the clinical medication rules of Chinese medicine in the treatment of early threatened abortion complicated with SCH. Based on literature search and combining descriptive analysis, association rule analysis and cluster analysis, the paper discussed the medication rules of TCM in the treatment of early threatened abortion complicated with SCH, so as to provide reference and further research direction for the treatment of early threatened abortion with SCH with TCM.

DATA AND METHODS

Literature Resources

Literature searching was performed in China journal full-text database (CNKI), ten thousand full-text database (Wanfang Data), Chinese Periodical Service Platform (VIP), Chinese Biomedical Medical Literature Database (CBM) and PubMed, Embase. The limited language sources were Chinese and English literature. The search start time was unlimited, and the deadline was May 28, 2021.

Inclusion Criteria

(1) Prescriptions of TCM in the treatment of early threatened abortion merger SCH literature; (2) The clinical literature on the treatment of early threatened abortion combined with SCH contained TCM prescriptions; (3) Introduction of expert experience and medical records on the treatment of threatened abortion with SCH with TCM; (4) The taste of the prescription is specific and complete; (5) The method of administration is oral, satisfying the condition.

Exclusion Criteria

(1) Review, system evaluation, meta analysis, news, reviews, protocol, animal experiments, case

observation, case report; (2) The use of single medicine or prescription is incomplete; (3) Capsules, pills, injections, plasters; (4) Literature related to ethnic minority medicine, such as Tibetan medicine and Miao medicine; (5) Only one of the multiple literatures on the same Chinese medicine prescription.

Literature Quality Control

According to the inclusion criteria and exclusion criteria, literature quality control conducted respectively by two data entry, and they may check each other to ensure the completeness and accuracy of data entry. If there was any objection, they would be jointly discussed. If the opinions were inconsistent, the third party would review and proofread to ensure its accuracy. After the data entry, the problems in the process of data entry were normalized again to ensure the quality of the literature extraction data.

Data Specification and Input

With input of TCM standardization processing refer to ordinary higher education teaching material of "twelfth five-year" national planning "Chinese Materia Medica" and the *Pharmacopoeia of the People's Republic of China* (2020 Edition) to the name of the prescription of TCM, efficacy, property and flavour, the normalization processing. The same drugs are not differentiated by region, processing method and other names, and are standardized as unified drug names, such as Jiangbanxia (*Pinellia ternata* (Thunb.) Breit., 姜半夏), Fabanxia (*Rhizoma Pinellinae Praeparata*, 法半夏), and Zhibanxia (*Making Pinellia ternata*, 制半夏) were unified as Banxia (*Rhizoma Pinellinae Praeparata*, 半夏). Jinyinhuan (*Honeysuckle charcoal*, 金银花炭), Shuanghua (*Lonicera japonica* Thunb., 双花) and Shuanghuan (*Double flower charcoal*, 双花炭) were unified as Jinyinhua (*Honeysuckle flower*, 金银花) and Ejiao beads were unified as Ejiao, but for those with large differences recorded as different drugs, such as Shengdihuang (*Radix Rehmanniae*, 生地黃) and Shudihuang (*Rehmannia Preparata Radix*, 熟地黃), Jiudahuang (*Prepared Radix et Rhizoma Rhei with Wine*, 酒大黃) and Dahuangtan (*Charread Radix et Rhizoma Rhei*, 大黃炭); Removal of medicinal modifier, the micro data specification, mild cold and mild sweetness as cold and sweet.

Data Processing and Statistical Analysis

The two researchers established clinical literature database with NoteExpress software respectively, extracted relevant data and entered it into Microsoft Excel files. Then, association rules of high-frequency TCM were analyzed with Apriori algorithm of IBM SPSS Modeler 18.0 software. The minimum support degree was set as 10%, the minimum confidence degree as 80%, the maximum first item as 5, and the elevation degree was greater than 1, so as to explore the drug use rule of TCM in the treatment of early threatened abortion complicated with subchorionic hematoma. SPSS Statistics 23.0 was used to systematically cluster drugs with high statistical frequency, and Pearson correlation coefficient was used to measure the similarity between variables.

RESULTS

Literature Screening Results

Through searching 6 databases, a total of 1,924 articles were retrieved, including 500 CNKI articles, 665 Wanfang Data articles, 454 VIP articles, 251 CBM articles, 31 PubMed articles and 23 Embase articles. All the literatures were imported into NoteExpress software to remove duplicate literatures. By reading the title, abstract and full text of the literatures, the prescriptions were screened according to the inclusion and exclusion criteria, and 100 eligible literatures were finally selected.

Descriptive Analysis Results

Frequency analysis of TCM

After sorting out the 100 literatures searched in this paper, 114 Chinese herbs flavors were involved, and the frequency of use was 1,286 times. In the treatment of early threatened abortion combined with SCH, a total of 28 Chinese herbs were used more than 10 times, and the frequency from high to low was Xuduan (*Radix dipsaci*, 续断), Tusizi (*Semen Cuscutae*, 菟丝子), Sangjisheng (*Herba Taxilli*, 桑寄生), Baizhu (*Rhizoma Atractylodis Macrocephalae*, 白术), Huangqi (*Astragalus membranaceus*, 黄芪), Baishao (*Radix paeoniae*, 白芍), Ejiao (*Colla Corii Aaini*, 阿胶), Huangqin (*Radix scutellariae*, 黄芩), Xianhecao (*Herba Agrimoniae*, 仙鹤草), Dangshen (*Radix Codonopsis*, 党参), etc., as shown in Table 1.

Analysis of drug efficacy

According to the efficacy classification

Table 1. Analysis Results of Chinese Medicines for Early Threatened Abortion with SCH ≥ 10 Times

No.	Name of Drugs	Use time	Frequency
1	Xuduan	87	87%
2	Tusizi	86	86%
3	Sangjisheng	84	84%
4	Baizhu	77	77%
5	Huangqi	63	63%
6	Baishao	53	53%
7	Ejiao	52	52%
8	Huangqin	49	49%
9	Xianhecao	48	48%
10	Dangshen	47	47%
11	Gancao (<i>Radix</i> , 甘草)	46	46%
12	Duzhong (<i>Eucommia</i> , 杜仲)	44	44%
13	Danggui (<i>Angelica</i> , 当归)	43	43%
14	Zhumagen (<i>Ramie root</i> , 苎麻根)	33	33%
15	Sanqi	31	31%
16	Mohanlian (<i>Eclipta</i> , 墨旱莲)	26	26%
17	Danshen (<i>Salvia miltiorrhiza</i> , 丹参)	24	24%
18	Shanyao (<i>Yam</i> , 山药)	24	24%
19	Shengdihuang	19	19%
20	Diyu (<i>Ulmus</i> , 地榆)	17	17%
21	Shengma (<i>Rhizoma cimicifugae</i> , 升麻)	17	17%
22	Baiji (<i>Bletilla striata</i> , 白芨)	15	15%
23	Shudihuang	14	14%
24	Oujie (<i>Lotus root section</i> , 藕节)	13	13%
25	Taizishen (<i>Pseudostellaria</i> , 太子参)	12	12%
26	Chuanxiong (<i>Ligusticum wallichii</i> , 川芎)	10	10%
27	Puhuang	10	10%
28	Qiancao	10	10%

Note: Frequency is the number of the occurrence of the drug in the first 100 prescriptions; Use frequency = frequency/number of prescriptions $\times 100\%$

standard of TCM, a national textbook of the 12th Five-Year Plan for general higher education, 114 Chinese herbs were classified and analyzed, and it was found that the main drugs for treating early threatened abortion combined with SCH were deficiency tonifying drugs, hemostatic drugs and heat-clearing drugs, as shown in Table 2.

Property statistics of TCM

Herbal medicinal statistics of Chinese medicine can be divided by quantity of cold, warm, cold, each corresponding to a kind of Chinese traditional medicine blindly medicinal properties. The total frequency of 114 Chinese herbs in the treatment of early threatened abortion combined with SCH was

Table 2. Efficacy Classification of Chinese Medicine for Early Threatened Abortion Combined with Subchorionic Haematoma

Efficacy	No. of herbs	Usage times (n)	Frequency (%)
Deficiency tonifying drugs	29	709	55.13
Hemostatic	18	210	16.33
Heat-clearing drugs	20	116	9.02
Removing wind-dampness drugs	3	87	0.23
Circulation and removing blood stasis	11	55	4.28
Antipyretic drugs	4	27	2.10
Astringent drugs	9	25	1.94
Qi-regulating drugs	6	21	1.63
Tranquilizers	6	10	0.78
Damp-clearing drugs	2	9	0.70
Water-clearing and dampness-clearing drugs	1	7	0.54
Liver-calming wind-extinguishing drugs	2	6	0.47
Antiasthmatic drugs	2	3	0.23
Purgative drugs	1	1	0.08

1,286 times. Among them, the highest frequency of use was flat medicine 474 times (36.86%), followed by warm medicine 459 times (35.69%), cold medicine 340 times (26.44%), and cold medicine 4 times (1.01%). According to the taste of Chinese medicine, it can be divided into 7 kinds: sour, bitter, sweet, pungent, salty, light and acerbity. According to the statistics of 114 Chinese herbs in the treatment of early threatened abortion combined with SCH, the highest frequency of use was sweet 859 times (66.80%), bitter 639 times (49.69%), pungent 306 times (23.79%), etc., as shown in Table 3.

According to the statistics of Zang-fu channel reduction in the treatment of threatened abortion with SCH, the top 3 channels were liver channel 868 times

(67.50%), spleen channel 592 times (45.96%), kidney channel 541 times (42.07%), as shown in Table 4.

Table 4. TCM Treatment of Early Threatened Abortion Combined with Subchorionic Haematoma Channel Tropism of Traditional Chinese Medicines on Statistics

Channel Tropism	Number of Herbs	Use times	Frequency (%)
Liver	74	848	65.94
Spleen	37	597	46.42
Kidney	46	547	42.53
Lung	34	400	31.10
Heart	38	292	22.71
Stomach	26	252	19.60
Large intestine	20	114	8.86
Gallbladder	7	74	5.75
Small intestine	3	55	4.28
Xinbao	6	29	2.26
Bladder	6	14	1.09
Sanjiao	2	5	0.39

Analysis of high-frequency drug association rules

IBM SPSS Modeler 18 was used for drug association rule analysis. Association rules have three indicators to measure the strength of the rules, including support, confidence and promotion. Support indicates the probability that two drugs will be used together. Confidence is the probability that drug A is used and drug B is also used. Elevation is the ratio of the probability that drug B will be used at the same time with drug A to the probability that drug B will be used without drug A. Set the minimum condition support of 10%, the minimum rule confidence of 50%, the maximum number of previous items to 5, and the enhancement degree to greater than 1, and conduct association rule analysis for drugs. According to Apriori algorithm, the network diagram between drugs was shown in Figure 1. The association rules were shown in Table 5, Table 6 and Table 7.

Table 3. Statistics of Four Qi and Five Taste of Subchorionic Haematoma Chinese Medicine in the Treatment of Early Threatened Abortion

Four qi	Herbs number	Use time	Frequency (%)	Taste	HerbNumber	Use time	Frequency (%)
Gentle	34	474	36.86	Sweet	64	859	66.80
Warm	38	459	35.69	Bitter	37	639	49.69
Cold	38	340	26.44	Pungent	25	306	23.79
Cool	4	13	1.01	Acerbity	18	128	9.95
				Sour	10	110	8.55
				Salty	7	22	1.71
				Light	2	8	0.62

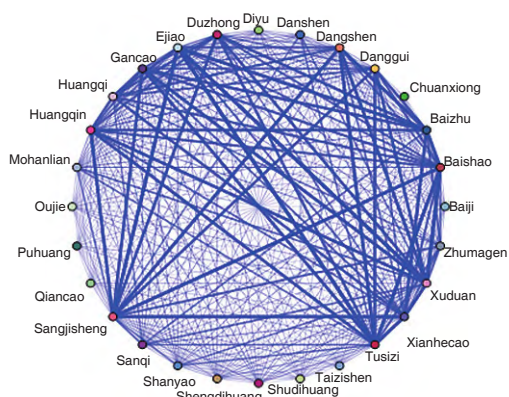


Figure 1. Subchorionic Haematoma Commonly Used Drug Combination Network in TCM Treatment of Early Threatened Abortion

Table 5. Results of Binomial Association Rules Analysis of Early Threatened Abortion with Subchorionic Haematoma High Frequency Use of Traditional Chinese Medicine Previous Item Support Percentage Confidence Percentage

No.	Consequene	Former term	Support percentage (%)	Confidence percentage (%)
1	Tusizi	Xuduan	86.14	91.95
2	Sangjisheng	Xuduan	86.14	88.51
3	Xuduan	Tusizi	85.15	93.02
4	Sangjisheng	Tusizi	85.15	91.86
5	Baizhu	Tusizi	85.15	81.40
6	Tusizi	Sangjisheng	83.17	94.05
7	Xuduan	Sangjisheng	83.17	91.67
8	Baizhu	Sangjisheng	83.17	80.95
9	Tusizi	Baizhu	76.24	90.91
10	Sangjisheng	Baizhu	76.24	88.31
11	Xuduan	Baizhu	76.24	88.31
12	Xudan	Huangqi	62.38	95.24
13	Sangjisheng	Huangqi	62.38	90.48
14	Tusizi	Huangqi	62.38	90.48
15	Baizhu	Huangqi	62.38	87.30
16	Xuduan	Baishao	52.48	90.57
17	Sangjisheng	Baishao	52.48	86.79
18	Tusizi	Baishao	52.48	86.79
19	Baizhu	Baishao	52.48	81.13
20	Tusizi	Ejiao	51.49	94.23

High-frequency drug cluster analysis

SPSS Statistics 23.0 was used to systematically cluster 28 high frequency drugs (use frequency ≥ 10 times) in the treatment of early threatened abortion complicated with SCH, and the drugs were divided into 7 effective clusters, which were: ① Tusizi-Sangjisheng-Xuduan-Ejiao- Baizhu-Dangsh; ② Xianhecao-Zhumagen-Huangqin-Duzhong-Huangqi-Shengma;

Table 6. Analysis Results of Three Association Rules for the Treatment of Early Threatened Abortion by Chinese Medicine Combined with Subchorionic Haematoma High Frequency Medication

No.	Consequent	Former term	Percentage of support (%)	Confidence percentage (%)
1	Sangjisheng	Tusizi and Xuduan	79.21	93.75
2	Baizhu	Tusizi and Xuduan	79.21	80.00
3	Xuduan	Sangjisheng and Tusizi	78.22	94.94
4	Baiz	Sangjisheng and Tusizi	78.22	81.01
5	Tusizi	Sangjisheng and Xuduan	76.24	97.40
6	Sangjisheng	Baizhu and Tusizi	69.31	91.43
7	Xuduan	Baizhu and Tusizi	69.31	91.43
8	Tusizi	Baizhu and Sangjisheng	67.33	94.12
9	Tusizi	Baizhu and Xuduan	67.33	94.12
10	Xuduan	Baizhu and Sangjisheng	67.33	89.71
11	Sangjisheng	Baizhu and Xuduan	67.33	89.71
12	Tusizi	Huangqi and Xuduan	59.41	93.33
13	Sangjisheng	Huangqi and Xuduan	59.41	90.00
14	Baizhu	Huangqi and Xuduan	59.41	
15	Xuduan	Huangqi and Tusizi	56.44	98.25
16	Tusizi	Huangqi and Sangjisheng	56.44	94.74
17	Sangjisheng	Huangqi and Tusizi	56.44	94.74
18	Xuduan	Huangqi and sangjisheng	56.44	94.74
19	Baizhu	Huangqi and sangjisheng	56.44	87.72
20	Baizhu	Huangqi and Tusizi	56.44	87.72

③ Baishao-Gancao-Danggui-Shudihuang; ④ Sanqi-Baiji; ⑤ Mohanlian-Diyu-Shanyao-Shengdihuang-Taizishen-Danshen; ⑥ Oujie; ⑦ Puhuanh-Qiancao. The tree diagram of cluster analysis was shown in Figure 2.

DISCUSSION

Liver, Spleen and Kidney Damaged, Stasis and Heat Disturbance and Chongren Deficiency

Early threatened abortion combined with subchorionic hematoma belongs to the category of "fetal leakage" and "fetal disturbance" in Chinese medicine. Its main pathogenesis is Chongren injury and weak embryo,^[6] and Chongren is closely related to liver, spleen and kidney.^[7] Wang Junling believes that subchorionic hematoma belongs to the blood from the menstrual cycle and belongs to the category of "blood stasis" in TCM.^[8] Professor Zhang Yuzhen^[9] believes that "blood stasis" is formed at a certain stage in the pathological process of abortion due to the differences in deficiency, excess, cold, heat, chronic illness or kidney deficiency constitution.

Table 7. Analysis Results of Four Association Rules for the Treatment of Early Threatened Abortion by TCM Combined with Subchorionic Haematoma High Frequency Medication

No.	Consequent	Antecedent	Percentage of support (%)	Confidence Percentage (%)
1	Baizhu	Sangjisheng and Tusizi and Xuduan	74.26	80.00
2	Xuduan	Baizhu and Sangjisheng and Tusizi	63.37	93.75
3	Sangjisheng	Baizhu and Tusizi and Xuduan	63.37	93.75
4	Tusizi	Baizhu and Sangjisheng and Xuduan	60.40	98.36
5	Sangjisheng	Huangqi and Tusizi and Xuduan	55.45	94.64
6	Baizhu	Huangqi and Tusizi and Xuduan	55.45	87.50
7	Xuduan	Huangqi and Sangjisheng and Tusizi	53.47	98.15
8	Tusizi	Huangqi and Sangjisheng and Xuduan	53.47	98.15
9	Baizhu	Huangqi and Sangjisheng and Tusizi	53.47	87.04
10	Baizhu	Huangqi and Sangjisheng and Xuduan	53.47	87.04
11	Xuduan	Huangqi and Baizhu and Tusizi	49.50	98.00
12	Tusizi	Huangqi and Baizhu and Sangjisheng	49.50	94.00
13	Sangjisheng	Huangqi and Baizhu and Tusizi	49.50	94.00
14	Xuduan	Huangqi and Baizhu and Sangjisheng	49.50	94.00
15	Sangjisheng	Ejiao and Tusizi and Xuduan	47.52	91.67
16	Baizhu	Ejiao and Tusizi and Xuduan	47.52	83.33
17	Tusizi	Ejiao and Sangjisheng and Xuduan	44.55	97.78
18	Baizhu	Ejiao and Sangjisheng and Xuduan	44.55	84.44
19	Xuduan	Ejiao and Sangjisheng and Tusizi	43.56	100.00
20	Baizhu	Ejiao and Sangjisheng and Tusizi	43.56	84.09

When the fetus is restless due to "blood stasis", which is both the cause and the product of pathology, and often cause and affect each other. Blood stasis blocks the uterine cell, and Chong Ren is not smooth. Qi and blood could not reach the uterine cell and cause fetal restlessness. Therefore, for early threatened abortion with SCH, attention should be paid to the factor of blood stasis. The common factors affecting Chongren injury, in addition to the liver, spleen and kidney, blood stasis, Professor Zhang Yuzhen

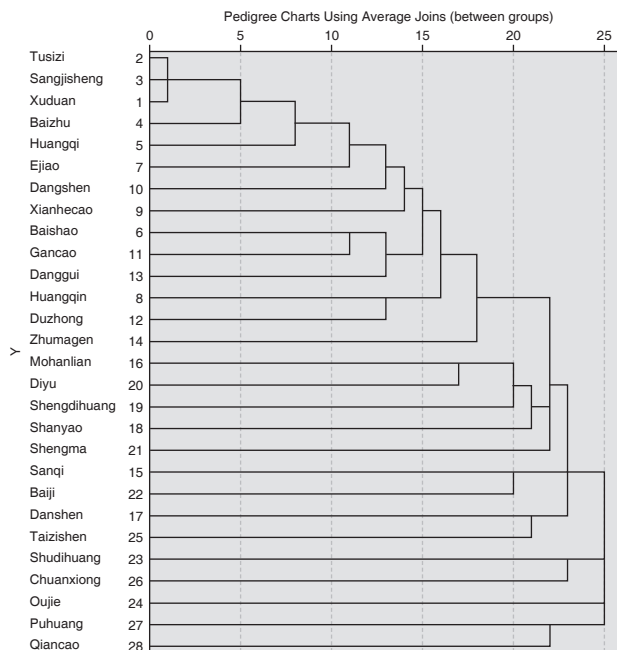


Figure 2. Tree Diagram of Subchorionic Haematoma High Frequency Drug Cluster Analysis in the Treatment of Early Threatened Abortion by TCM

believes that there is blood heat.^[6] *Jingyue Book• Women Rules* <<景岳全书•妇人规>> said: "all fetal heat, blood easy to move, blood movement, fetal restfulness." So the miscarriage prevention should pay attention to clearing heat. In conclusion, the main pathogenesis of early threatened abortion combined with SCH is Chongren injury, fetal element not solid, related to liver, spleen and kidney. The kidney deficiency, blood stasis and blood heat are important pathogenic factors. Treatment should be to tonify liver and kidney, invigorate spleen qi and blood, clear heat and blood stasis.

The Primary Function of Shoutai Pill to Tonify the Kidney and Regulate the Chong Ren, A Special Formula Designed to Promote the Healthy Development of the Fetus

In this study, the frequency of drug use was ranked from high to low, and the results showed that the top 10 Chinese herbs were Xuduan, Tusizi, Sangjisheng, Baizhu, Huangqi, Baishao, Ejiao, Huangqin, Xianhecao, Dangshen. It can be seen that the high-frequency drugs are mainly used in Shoutai pills, and commonly used products for strengthening spleen and qi, tonifying kidney and spleen, and appropriately accompanied by clearing heat and stopping bleeding. From Table 2, the treatment of early threatening abortion combined with subchorionic

hematoma drug efficacy to the liver, spleen and kidney tonifying drugs, which tonifying deficiency drugs and intermittent, Tusizi, Sangjisheng, such as tonifying liver and Ejiao, Dihuang nourishing blood, Huangqi, Baizhu, Dangshen, etc. tonifying qi and spleen, tonifying kidney and spleen nourishing qi and blood, is the treatment of fetal restfulness. The top three of Zang-fu channels were liver, spleen and kidney (Table 4). This is in line with the pathogenesis of SCH, involving the kidney, spleen, liver three viscera, kidney for the congenital, the main reproduction, the main collection of essence and the system of births, kidney-qi flourishing itself can shadow the fetus, and spleen for the acquired, the source of qi and blood biochemistry. Qi can carry the fetus, blood can nourish the fetus, liver storage of blood, the main drainage, and Chong Ren two veins are closely related. Kidney qi kidney qi plenty, liver spleen regulation, Chong Ren patency, then the embryo is stable. Tusizi, Xuduan, Sangjisheng, and Ejiao are the ingredient of the Shoutai Pill, from Zhang Xichun's *Yi Xue Zhong Zhong Can Xi Lu* <<医学衷中参西录>>, originally was designed for the habitual abortion, the function of tonifying kidney qi, solid Chong Ren safe fetus.

Association rules were analyzed for high frequency drugs. Table 5, 6 and 7 showed that among the results of binomial association rules analysis. The Chinese medicine combination of "Tusizi-Xuduan" had the highest support, followed by the Chinese medicine combination of "Sangjisheng-Xuduan", "Xuduan-Tusizi" and "Sangjisheng-Tusizi", and the Chinese medicine combination of "Sangjisheng-Tusizi-Xuduan" had the highest support. Among the four association rules, the highest degree of support was "Sangjisheng-Tusizi-Xuduan-Baizhu", and the highest degree of confidence was "Ejiao-Sangjisheng-Tusizi-Xuduan-Baizhu" combination. Among the Chinese medicine combinations with the highest degree of support for two, three and four associations, the efficacy is mainly to tonifying liver and kidney and spleen. Among the four combinations, the drug combination with the highest degree of confidence is the original prescription of Zhang Xichun Shoutai Pill, which is the basic prescription of fetal protection and widely used in clinical fetal protection.

Shoutai Pills (寿胎丸) was further modified by

Professor Luo Yuankai into Zishen Yutai Pills (滋肾育胎丸). The Meta^[10] analysis showed that the oral administration of Zishen Yutai Pills (滋肾育胎丸), as a supplementary therapy, could significantly improve the human chorionic gonadotropin, progesterone, estradiol and fibrinogen indexes and symptoms of abdominal pain and vaginal bleeding in early SCH patients. Clinical randomized controlled trials have shown that Zishen Yutai Pill can increase the live birth rate after fresh embryo transfer compared with placebo. Animal experiments^[11] have found that Shoutai Pills can improve endometrial receptivity by increasing the expression of endometrial integrin $\beta 3$ and LIF during the implantation window. In combination with UHPLC-Q-TOF-MS^[12] and network pharmacological analysis,^[13] Zishen Yutai Pills was found to regulate neuroactive ligand-receptor interactions, steroid hormone biosynthesis and ovarian steroid production as its potential mechanisms.

With Clearing Heat and Cooling Blood, Fetal Yuan Peaceful

In addition to deficiency, fetal movement also has an important complex factor of lower lower-jiao blood heat, heat disturbance fetal element, so Huangqin, Shengdihuang, Huangbai (*Cortex Phellodendri Chinsis*, 黄柏), Danpi (*Cortex Moutan*, 丹皮) and other heat-clearing and blood-cooling drugs are also widely used in SCH. *Tai Chan Jiyao* <<胎产集要>> said: "Baizhu benefits the spleen to cultivate the mother of all things, and Huangqin purifies fire to nourish the Yin of the child's household, so it is said to be sacred medicine for fetal peace", covering Yin blood accumulation after pregnancy to nourish the fetus, coupled with modern lifestyle pregnant women more worry about fatigue and Yin blood, the body Yin deficiency Yang heat excessive, heat disturbance Chong Ren, fetal Yuan restless. At this time, Yin and blood deficiency is not the basis, and heat disturbance leakage is the standard. Huangqin bitter cold and Huangqin is designed to clear the evil heat, make the blood not go wrong, and use Baizhu to strengthen spleen and remove dampness and heat without the harm of bitter cold. So does not stop bleeding and stop itself fetal Yuan would be peaceful.

Supplement with Blood Circulation to Remove Blood Stasis to New Birth of the Fetus

SCH belongs to the category of Chinese

medicine "blood stasis", belongs to the blood from the meridian, the blood stasis does not go to the Chong Ren impasses, "blood stasis does not go, new blood is not born", the fetus is displaced, at this time must not remove blood stasis and placenta. In the treatment of early threatened abortion complicated with subchorionic hematoma, syndrome differentiation and hemostasis is the key. It is necessary to remove stasis and hemostasis, to remove blood stasis, to create new blood, to remove stasis and collaterals, to Chongren fluent, to nourish the fetus, then the fetus is safe. Clinically, it can not be confined to abortion and fear, the so-called "there is no death, is no death also". *Jing Xiao Chan Bao* <<经效产宝>> said: "The fetus was aborted under the blood, uterus dry led to death, should be treated urgently." Among the first 28 kinds of high-frequency drugs, the drugs for promoting blood circulation and removing blood stasis include Danggui, Chuanxiong and Danshen, the drugs for removing blood stasis include Sanqi, Puhuang and Qiancao, and the drugs for nourishing Yin and clearing heat and stopping bleeding include Ejiao, Baiji, Xianhecao, Zhumagen, Diyu and Oujie. Clinical studies have found^[14] that the method of promoting blood circulation and removing blood stasis can improve the hypercoagulable state of blood during pregnancy, and is conducive to reducing the abortion rate of patients with PTS complicated with thrombosis. In addition, it has been found in clinical studies^[15] that in the treatment of SCH in pregnancy, the combination of kidney-invigorating and blood-activating prescription and low molecular weight heparin can lower the D-dimer and homocysteine levels of patients, reduce the area of subchorionic hematoma, and accelerate the time of hematoma disappearance than the combination of progesterone and low molecular weight heparin. For SCH patients with blood stasis, it is necessary to "have the syndrome and use it as medicine". If the clinical application is afraid of promoting blood circulation and removing blood stasis, it is difficult to control and cause unnecessary disputes. At the same time, If the intensity of promoting blood circulation and removing blood stasis is strong in clinical application, it is difficult to control unnecessary disputes. At the same time of relieving the fetus and strengthening the body, the

appropriate use of blood stasis hemostatic drugs can stop bleeding without leaving blood stasis, remove blood stasis without injuring the body, and should stop the disease, so as to be safe and effective.^[16]

Combined with Pungent and Bitter, Sweet and Warm, Lifting Chong Ren Qi and Blood to Solid Fetus

As can be seen from Table 3, the main drugs for the treatment of early threatened abortion combined with subchorionic hematoma are Gentle, warm and cold. The five tastes are mainly sweet, bitter and pungent. Sweet "can supplement, can reconcile, can slow", which has the role of supplementing, mediating, harmonizing drug, slow pain. Bitter "can drain, can dry, can be firm", which has the role of clearing heat and draining fire, drying dampness, firm Yin. "Pungent" "can disperse, can promote the circulation of qi", which has the function of divergence, qi and blood. The smell is consistent, mainly with sweet and light, sweet and warm tonics, bitter cold and heat, pungent supplemented. Combined with the pathogenesis of early threatened abortion combined with SCH, it is advisable to supplement rather than attack, to clear rather than reduce, to cool rather than heat. In the prescription, it is peaceful, cold and warm, and strive to balance yin and yang. Considering the pathogenesis of early threatened abortion combined with subchorionic hematoma, it is appropriate to supplement rather than attack, to clear rather than purgative, to cool rather than heat, and to use prescription drugs to balance Yin and Yang and to combine cold and warm.^[17] The analysis of drug efficacy found that Shengma, Jingjietan (*Schizonepeta carbon*, 荆芥炭), Chaihu (*Bupleurum*, 柴胡) and Sangye (*Mulberry leaf*, 桑叶) were the four antipyretic drugs in the treatment of SCH, mainly Shengma (*Rhizoma cimicifugae*, 升麻), which could induce the sweet-warm drugs to rise, have the function of raising Yang and increasing the function of raising tonic drugs.

Paying Attention to the Pathogenesis Differentiation, Categorizing into Specific Formulation Clustering with a Specific Purpose Formulation

In conclusion, the main pathogenesis of early

threatened abortion combined with subchorionic hematoma is Chongren injury, fetal element is not solid, related to liver, spleen and kidney, mainly kidney deficiency, blood stasis and blood heat are important pathogenic factors. In treatment, the main diagnosis and treatment ideas are tonifying liver and kidney, invigorating spleen and replenishing qi and blood, clearing heat and removing blood stasis. Clustering results show that clinical medication is also this diagnosis and treatment idea: clustering (1): Tusizi-Sangjisheng-Xuduan-Ejiao-Baizhu-Dangshen, suitable for the weak of kidney deficiency and spleen, Shoutai Pill plus Baizhu, Dangshen, tonifying kidney and spleen, tonifying qi and nourishing blood. Clustering (2): Xianhecao-Zhumagen-Huangqin-Duzhong-Huangqi-Shengma combination, suitable for deficiency and abdominal fall, vaginal bleeding red color, Xianhecao convergence hemostasis, Zhumagen nourishing Yin and clearing heat to hemostatic solid embryo, Huangqin clearing heat, and with Duzhong to benefit kidney, and Huangqi and Shengma to tonify Qi to strengthen solid prophylaxis. Clustering (3): Baishao-Gancao-Danggui-Shudihuang, to reduce Chuanxiong on the basis of Siwu Decoction (四物汤) to prevent the circulation of blood and blood, to cooperate with Baishao, Gancao, for Shaoyao Gancao decoction (芍药甘草汤), with blood collection and Ying, slow and urgent pain. Shudihuang tonifying kidney filling essence, nourishing Yin blood, Danggui tonifying blood and blood circulation, the four medicines match, tonifying blood tonifying liver and kidney, and has the function of nourishing blood stasis, suitable for blood deficiency with blood stasis, pregnancy abdominal pain. Cluster (4): Sanqi-Baiji combined use, Sanqi, good blood stasis hemostasis, blood circulation and pain relief, Baiji striata convergence hemostasis. The two medicines are compatible with each other, restrict and promote each other, enhance the power of blood stasis, and match the obvious blood stasis signs with syndrome differentiation. Cluster (5): Mohanlian-Diyu-Shanyao-Shengdihuang-Taizishen (*Radix pseudostellariae*)-Danshen combined, Mohanlian has the function of nourishing liver and kidney, cooling blood and hemostasis, Shengdihuang clearing heat and cooling blood, nourishing Yin and promoting fluid. Taizishen supplementing qi and invigorating spleen

and nourishing Yin, Shanyao strengthening spleen and stomach, invigorating kidney qi, Danshen dispelling stasis and invigorating new, Diyu cooling blood and hemostasis, this group of drugs is suitable for those with blood stasis and blood stasis due to deficiency of liver and kidney Yin. Clustering (6): Oujie is a single group, both can converge hemostasis, and can remove blood stasis, with the characteristics of hemostasis without leaving stasis, *Compendium of Materia Medica* <<本草纲目>> said: "Oujie powder, open the phrenic, toning the waist kidney, and blood, disperse all blood stasis, all new blood." Can be dialectically compatible with slight blood stasis. (7) Puhuang-Qiancao, Puhuang can remove blood stasis and hemostasis, with hemostasis without stasis characteristics. *Jingyue Quanshu* <<景岳全书>> recorded: "Good hemostasis, cooling blood and promoting blood circulation, eliminating blood stasis... Through the woman's meridians, stop collapse in the belt under, irregular menstruation, pregnant woman fetal leakage." It can be used in patients with obvious blood stasis. Clinically, the above clustering group can be flexibly selected according to the syndrome type of TCM.

SHORTCOMINGS AND PROSPECTS

Based on literature search and combined with descriptive analysis, association rule analysis and cluster analysis, this study discussed the rules of TCM medication for the treatment of early threatened abortion complicated with SCH, and found that Shoutai Pill was the core prescription of SCH, supplementing the liver, spleen and kidney, combining the pathogenesis of blood heat and blood stasis, and taking supplementing the liver and kidney, invigorating the spleen and supplementing qi and blood, clearing heat and removing blood stasis as the main diagnosis and treatment ideas. Related cluster drugs can be selected for treating SCH according to specific syndromes, and the disease will stop immediately.

At present, there are still some shortcomings in this study. First, the quality of data source cannot be evaluated, and low quality literature may lead to data mining distortion. Second, there are some limitations in data specification and processing methods, and there is still no authoritative conclusion. Third, the

classification according to the efficacy of TCM, and the classification of some drugs and the actual effect in the prescription is not consistent, resulting in data results may be biased, such as Sangjisheng is a wind-dampness drug, the actual function of protecting the fetus to tonify the liver and kidney and tonify the deficiency. Shengma is a drug to relieve the surface, the actual function of lifting. Therefore, how to more scientifically and accurately explore the drug use rules of early threatened abortion combined with SCH by TCM needs further research.

REFERENCES

1. Feng YJ, Shen K. Gynecology and Obstetrics. 1st edition. Beijing: People's Medical Publishing House, 2012: 67.
2. Dogra V, Paspulati RM, Bhatt S. First Trimester Bleeding Evaluation. *UltrasoundQ*, 2005, 21(2): 69-85.
3. Fu YB, Du HC, Ruan YW. Pregnancy outcome of threatened abortion complicated with subchorionic hematoma. *Chinese Journal of Family Planning*, 2002, 10(2): 113-115.
4. Li Q, Zhu J, Hua KQ. A meta-analysis of pregnancy outcomes in pregnant women with subvillous hematoma. *Chinese Journal of Medicine*, 2016, 96(17):1383-1385.
5. Lu Y, Li H, Li XH. Analysis of pregnancy outcomes of 293 cases of threatened abortion complicated with subvillous hematoma. *Jilin Medicine*, 2015, 36(12):2453-2455.
6. Zhang YZ. *Chinese Gynecology*. 2nd Ed. Beijing: China Traditional Chinese Medicine Press, 2007:210-214.
7. Yin QZ, Hao XH, Gu HP. On women's treatment of Chong Ren and liver, spleen and kidney. *Sichuan Journal of Traditional Chinese Medicine*, 2010, 28(4): 28-29.
8. Liu YL, Ning Y, Teng H. Wang Junling's experience in treating early threatened abortion complicated with subchorionic hematoma with gelatine decoction. *Chinese Medical Review*, 20, 17(29):139-142.
9. Lu RL, Tao LL, Li L. Professor Zhang Yuzhen's experience in abortion reform. *Hebei Journal of Traditional Chinese Medicine*, 2007, 29(7): 584-585.
10. Xu L, Tu Q, Wang F, et al. Zishen yutai pill as an adjuvant therapy in threatened Miscarriage: A meta-analysis of 23 randomized controlled trials. *Heliyon*, 2023; 9(6): e16213.
11. Chen X, Hao C, Deng W, et al. Effects of the Zishen Yutai Pill Compared With Placebo on Live Births Among Women in a Fresh Embryo Transfer Cycle: A Randomized Controlled Trial. *Obstet Gynecol*, 2022, 139(2): 192-201.
12. Chen XY, Chen J, Wang ZY, et al. Effects of modified Shoutaiwai recipe on integrin $\beta 3$ and leukemia-inhibitory factor in endometrium of controlled ovarian hyperstimulation mice during the implantation window. *Genet Mol Res*, 2015, 14(2): 2970-2977.
13. Dang L, Zhang C, Su B, et al. Mechanisms of action of Zishen Yutai pills in treating premature ovarian failure determined by integrating UHPLC-Q-TOF-MS and network pharmacology analysis. *BMC Complement Med Ther*, 2022, 22(1): 281.
14. Jiang XK, Yao JL, Gu Y. Treatment of 40 cases of early threatened abortion complicated with subchorionic hematoma by Bushen Huoxue Antai prescription combined with dydrogesterone. *Journal of Shandong University of Traditional Chinese Medicine*, 2009, 33(2):137-139.
15. Tao LL, Guo M, Lu GJ. Clinical observation of tonifying kidney and promoting blood circulation combined with low molecular weight heparin in the treatment of threatened abortion complicated with subchorionic hematoma. *Yunnan Journal of Traditional Chinese Medicine*, 2021, 42(9):49-51.
16. Zeng L. Clinical observation on the treatment of early threatened abortion complicated with subchorionic hematoma by invigorating kidney and invigorating spleen and removing stasis for fetal abortion. *Guangzhou: Guangzhou University of Traditional Chinese Medicine*, 2015.
17. Shen Y, Fu P. Study on the medication regularity of Fu Ping in the treatment of threatened abortion based on data mining. *Zhejiang Journal of Integrated Chinese and Western Medicine*, 2018, 28(1): 67-71.

(Received October 16, 2023)