

History of recurrent miscarriage in traditional Chinese medicine literature

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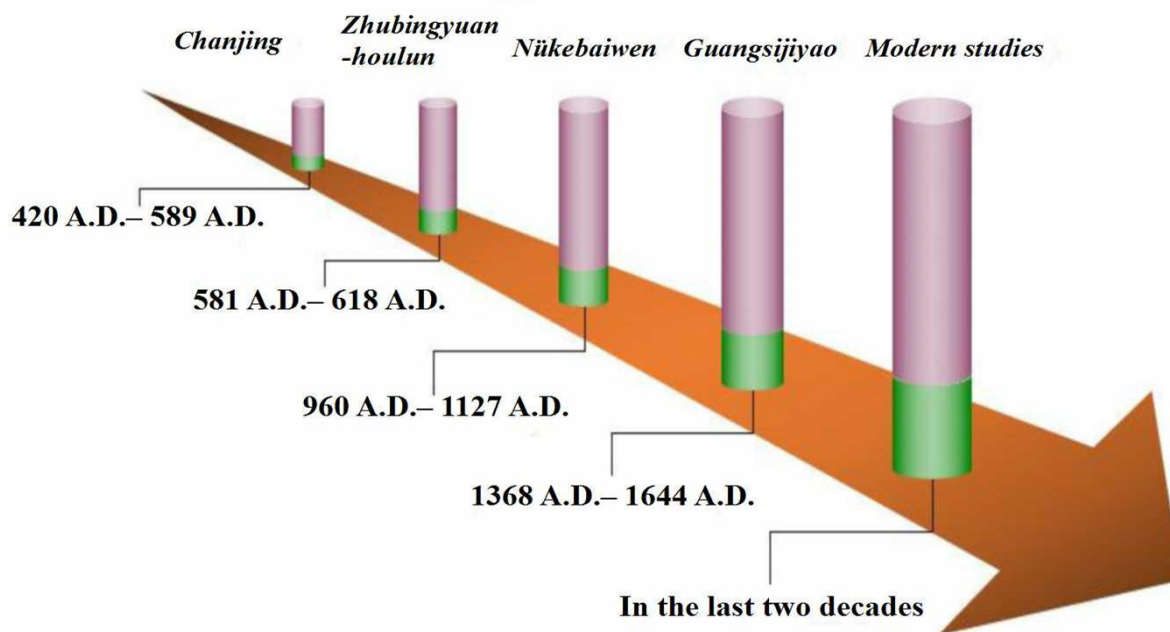
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Highlights

This report reviews the etiology, pathogenesis, treatment, and prevention of recurrent miscarriage discussed in the traditional Chinese medicine literature and lists the pharmacological studies that evaluated traditional Chinese medicine prescriptions for recurrent miscarriage.

Editor's Summary

The first cases of recurrent miscarriage as a fertility abnormality were reported in *Chanjing*, written during the Nanbei Dynasty of China (420 A.D. – 589 A.D.).



Historical records and modern researches on recurrent miscarriage

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Abstract

Recurrent miscarriage (RM) as a gynecological disorder was recognized by traditional Chinese medicine (TCM) practitioners long before the age of modern medicine. TCM physicians reported and recorded RM in the canonical TCM literature, which dates back more than 1500 years. The first cases of RM as a fertility abnormality were reported in *Chanjing*, which was written during the Nanbei Dynasty of China (420 A.D. – 589 A.D.). Some prescriptions for the treatment of RM are still actively used by modern TCM practitioners. In addition, many recent pharmacological and clinical studies have focused on the TCM therapy for RM. To identify the new therapeutic targets for RM and further promote the interest in treating RM with TCM, we reviewed the etiology, pathogenesis, treatment, and prevention of RM discussed both in the TCM literature and in contemporary pharmacological and clinical studies.

Keywords: Recurrent miscarriage, Traditional Chinese medicine, Literature

摘要

早在 1500 多年前，中医古籍对复发性流产就有相应的记载。最早把复发性流产当成生殖异常的记载出现在南北朝时期的古籍《产经》上 (420 A.D. – 589 A.D.)，许多治疗复发性流产的经典方剂沿用至今。本文回顾了历代医家对复发性流产的病因病机及治疗的认识，列出了中医治疗复发性流产的经典方，以及现代医学中关于复发性流产的药理学研究和临床研究。

关键词：复发性流产；中医；文献

Abbreviations: RM, Recurrent miscarriage; TCM, Traditional Chinese medicine.

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Background

Recent guidelines define recurrent miscarriage (RM) as a fertility defect in which two or more consecutive pregnancy losses occur before 20 weeks of gestation. Approximately 1-2% of women of reproductive age have this abnormality [1-3]. RM induces physical and psychological disorders in female patients, and it can even destabilize marriage and family, making it a considerable challenge for gynecologists. Therefore, studies on the prevention and treatment of RM have vital clinical and social importance. Traditional Chinese medicine (TCM) has been practiced in China for thousands of years. Recently, the treatment of diseases such as RM, leukemia, and malaria with TCM as a complementary therapy is getting more attention [4-12]. Although a wider clinical application of TCM is limited because of the lack of quantitative studies and systematic analyses, successful reports such as the discovery of arteannuin, the active ingredient of Qinghao (*Herba Artemisiae Annuae*), suggest that TCM remains a rich source of new therapeutic targets [8]. In this study, we summarized the information on RM in the TCM literature in chronological order to increase the understanding among conventional medicine practitioners.

Historical records in the TCM literature

The TCM theory was first described in the Chinese medicine classic book *Huangdineijing*. This book was a combined effort of many unknown authors from the Warring States period to the Han Dynasty of China (475 B.C. – 220 A.D.). This book contains two parts, *Suwen* and *Lingshu*. The book did not refer to RM as a disease but laid a solid foundation for the understanding of reproduction by correlating RM to the function of the kidneys. This concept is essential for all RM treatments in TCM. Chapter 1 of *Suwen* describes the strong association between the kidneys and reproduction during seven 7-year cycles, from childhood to the postmenopausal period (Table 1).

Despite its simplicity, this book is a comprehensive overview of the female reproductive cycle considering

the time it was written. Moreover, chapter 47 of *Suwen* stressed that “the meridian of the uterus is linked to the kidney” [13].

The first cases of RM as a fertility abnormality were reported in *Chanjing*, written during the Nanbei Dynasty of China (420 A.D. – 589 A.D.). Thereafter, RM was formally established as a disease by TCM practitioners and was studied more extensively in China. In *Chanjing*, RM was defined as multiple natural miscarriages, and Damaidoushi Decoction was recommended as a treatment, although this treatment was never prescribed in modern medicine. *Chanjing* acknowledged the importance of RM.

Another significant breakthrough in the treatment of RM was reported in the *Zhubingyuanhoulun* by Chao Yuanfang during the Sui Dynasty of China (581 A.D. – 618 A.D.), and this treatise was the first to describe the etiology and pathogenesis of RM. Miscarriage was discussed in detail in the chapter “Pregnancy with miscarriage”. It was suggested that deficiency of Qi and blood, in addition to kidney deficiency, led to the underdevelopment of the fetus and eventually miscarriage. The major reason for this pathogenesis is that the kidney controls the meridian of the uterus, and pregnant women with severe lumbago are at a high risk for natural miscarriage [14]. These views agreed with those proposed in *Huangdineijing* and established the primary etiology of RM.

The knowledge of gynecology and obstetrics in TCM was further popularized for the general public without a medical background in another classic book, *Nikebaiwen*, written by Qi Zhongfu in question and answer form during the Beisong Dynasty of China (960 A.D. – 1127 A.D.). Question 58 indicated that the occurrence of miscarriage usually at the same time of pregnancy was a key clinical feature of RM [15]. TCM practitioners during this period started to realize that it was essential to raise awareness in the general public about the early diagnosis, treatment, and prevention of RM. In this same period, Chen Ziming systematically summarized the medications contraindicated during pregnancy in *Furendaquanliangfang* as a form of RM prevention [16]. The information still serves as an important guidance in modern medicine for clinical use in pregnancy because of its comprehensiveness.

Table 1 7 cycles of female reproduction described in *Huangdineijing*

Age (year)	Phenomenon
7	The emanations of the kidney become abundant and promote the growths of hair and teeth.
14	Menstruation begins and the female is able to conceive.
21	The emanations of the kidney become regular and the female becomes sexually mature.
28	The female reaches the peak of all the physical features and the body is flourishing and fertile.
35	The physical conditions start to deteriorate including appearances of wrinkle and enhanced hair fall.
42	The physical appearance continues to decline.
49 and onwards	Menstruation stops and the female is no longer suitable to conceive due to hormonal and physical changes.



During the Ming Dynasty (A.D. 1368 – A.D. 1644) and the Qing Dynasty of China (A.D. 1644 – A.D. 1912), there was a greater understanding of the etiology, pathogenesis, treatment, and prevention of RM. In the Ming Dynasty of China (1368 A.D. – 1644 A.D.), Zhang Jingyue, a well-known TCM expert, published his lifetime experience in *Jingyuequanshu*, which contained 64 volumes [17]. It was a comprehensive publication in clinical practice, and part of the book was devoted to discussing the etiology, syndrome, pulse, therapeutic principle, and treatment of major gynecologic diseases. RM was described in detail in chapter 26, volume 38. Zhang presented the etiology and pathogenesis of RM in detail and observed that the underlying causes of RM were the deficiency of Qi, weak pulse, old age, emotional instability, lechery, falls, and improper diet. Second, Zhang proposed that RM should be treated with preventive therapy. This proposal agrees with current clinical practice where the body is recuperating before

pregnancy. Of note, Zhang developed two famous prescriptions for RM: Taiyuan Decoction and Taishanpanshi Powder (Table 2). These TCM prescriptions are the most common, have significant clinical efficacy, and are prescribed by TCM practitioners to date [18, 19]. Wan Quan, another famous physician during the Ming Dynasty of China (1368 A.D. – 1644 A.D.) also explained the etiology of RM in his publication, *Guangsijiyao*. He suggested that women who had RM tended to be emotionally unstable and consumed food that elicited strong responses from the body, leading to the damage of the Chong and Ren meridians [20]. These interpretations incorporate the concept of holism from the TCM theory, which regards the human body as a unity and postulates that body integrity is affected by many factors, including mood, diet, body shape, and the environment, all of which will eventually contribute to the disease state.

Table 2 Classic prescriptions treating recurrent miscarriage

Name	Origin	Function	Major ingredients
Taishanpanshi Powder	Zhang Jingyue, <i>Jingyuequanshu</i> , Ming Dynasty of China (1368 A.D. – 1644 A.D.)	Supplementing Qi to invigorate spleen and nourishing blood to prevent miscarriage	Xiyangshen (<i>Radix panacis ginseng</i>), Huangqi (<i>Radix astragali membranacei</i>), Danggui (<i>Radix angelicae sinensis</i>), Xuduan (<i>Radix dipsaci</i>), Huangqin (<i>Radix scutellariae baicalensis</i>), Chuanxiong (<i>Radix ligusticum wallichii</i>), Shudihuang (<i>Cooked radix rehmanniae</i>), Baizhu (<i>Rhizoma atractylodes macrocephalae</i>), Sharen (<i>Fructus amomi</i>), Gancao (<i>Radix glycyrrhizae</i>)
Taiyuan Decoction	Zhang Jingyue, <i>Jingyuequanshu</i> , Ming Dynasty of China (1368 A.D. – 1644 A.D.)	Tonifying kidney to prevent miscarriage	Xiyangshen (<i>Radix panacis ginseng</i>), Danggui (<i>Radix angelicae sinensis</i>), Duzhong (<i>Cortex eucommiae ulmoidis</i>), Baishao (<i>Radix albus paeoniae lactiflorae</i>), Shudihuang (<i>Cooked radix rehmanniae</i>), Baizhu (<i>Rhizoma atractylodes macrocephalae</i>), Gancao (<i>Radix glycyrrhizae</i>), Chenpi (<i>Percarpium citri reticulatae</i>)
Shoutai Pill	Zhang Xichun, <i>Yixue-zhongzhongcaxilu</i> , Qing Dynasty of China (1644 A.D. – 1912 A.D.)	Tonifying kidney to prevent miscarriage	Tusizi (<i>Semen cuscutae</i>), Banlangen (<i>Radix loranthis seu visci</i>), Xuduan (<i>Radix dipsaci</i>), Ejiao (<i>Gelatinum corii asinii</i>)
Andianertian Decoction	Fu Qingzhu, <i>Fuqingzhunikei</i> , Qing Dynasty of China (1644 A.D. – 1912 A.D.)	Nourishing spleen and tonifying kidney	Xiyangshen (<i>Radix panacis ginseng</i>), Shudihuang (<i>Cooked radix rehmanniae</i>), Baizhu (<i>Rhizoma atractylodes macrocephalae</i>), Shanyao (<i>Radix dioscoreae oppositae</i>), Shanzhuyu (<i>Fructus corni officinalis</i>), Gancao (<i>Radix glycyrrhizae</i>), Duzhong (<i>Cortex eucommiae ulmoidis</i>), Gouqizi (<i>Fructus lycii</i>), Baibiandou (<i>Semen dolichoris lablab</i>)



Table 3 Modern prescriptions for recurrent miscarriage

Reference	Prescription	Subject	Sample content		Function
			Experiment group	Control group	
Li <i>et al.</i> 1998 ²⁵	Bushenjianpi Recipe	Rat	8	8	Ameliorate the luteal function
Cao <i>et al.</i> 2001 ²⁶	Yiqiyangxue Recipe	Rat	6 (high dose) 8 (moderate dose) 7 (low dose)	8	Reduce the level of anti-trophoblastic cells and interleukin-2
Luo <i>et al.</i> 2003 ²⁷	Zhuyun No.3 Recipe	Rat	16	13	Up-regulate the expression of progesterin receptor; Relax the uterine smooth muscle
Liu <i>et al.</i> 2007 ²⁸	Bushenyiqi Recipe	Mice	6	6	Up-regulate the expression of progesterin receptor
Liu <i>et al.</i> 2008 ²⁹	Shoutai Pill	Mice	10 (high dose) 10 (moderate dose) 10 (low dose)	10	Down-regulate the expression of the protein of suppressor of cytokine signaling-1
Zeng 2009 ³⁰	Zhuyun No.3 Recipe	Rat	10 (high dose) 10 (moderate dose) 10 (low dose)	10	Up-regulate the expression of cytotoxic T cell lymphocyte antigen, interleukin-4 and interleukin-10 at maternal-fetal interface
Cao <i>et al.</i> 2011 ³¹	Bushenjianpi Recipe	Rat	10	10	Increase the expression of leukemia inhibitory factor and improve the endometrial receptivity
Tan <i>et al.</i> 2013 ³²	Shoutai Pill	Mice	10	10	Up-regulate the expression of annexin A in decidua
Li <i>et al.</i> 2014 ³³	Shoutai Pill	Mice	10 (high dose) 10 (moderate dose) 10 (low dose)	10	Up-regulate the expression of transferrin; Down-regulate the expression of heat shock protein 27
Li <i>et al.</i> 2015 ³⁴	Bushenjianpi Recipe	Mice	17	17	Up-regulate the expression of vascular endothelial growth factor and microvessel density in decidua



During the Qing Dynasty of China (1644 A.D. – 1912 A.D.), Huatai, the terminology of RM in TCM, was first described in two books, *Yizongjingjian* by Wu Qian and *Yeshinükezhengzhi* by Ye Tianshi [21, 22]. Huatai is widely accepted by TCM practitioners and is found in contemporary textbooks [23]. Zhang Xichun, a renowned physician during the Qing Dynasty of China (1644 A.D. – 1912 A.D.), was the first to combine TCM and conventional medicine. He described a standard prescription for RM, Shoutai Pill, in his representative work, *Yixuezhongzhongcanxilu*. This prescription is considered highly effective and is still widely used in clinical practice [24] (Table 2). Modern pharmacological studies on animal models identified mechanisms that could explain the effect of this therapy on RM [25-34] (Table 3). The ingredients of the Shoutai Pill include Tusizi (*Semen cuscatae*), Banlangen (*Radix loranthi seu visci*), Xuduan (*Radix dipsaci*), and Ejiao (*Gelatinum corii asinii*). In another book from the same period, *Fuqingzhunike*, the author Fu Qingzhu emphasized the importance of organs essential for metabolism, including the liver, spleen, and kidney, in the pathogenesis of gynecologic diseases [35]. The recommended prescription for RM was the Andianertian Decoction (Table 2). The theoretical basis of this therapy was related to the function of the kidney and spleen in TCM theory. According to TCM, the kidney governs the congenital constitution whereas the spleen governs the acquired constitution. If the congenital and acquired constitutions are stable, the fetus will develop normally and vice versa. Another pioneering anatomist and TCM practitioner during the Qing Dynasty of China (1644 A.D. – 1912 A.D.), Wang Qingren, correlated RM to blood circulation. He proposed the theory of “Blood Stasis Causing Disease” and developed standard prescriptions for improving blood circulation and reducing stasis [36]. The prescription was discussed in his major work, *Yilingaicao*. Wang suggested that RM was caused by blood stasis, and treatment should be based on the improvement of blood circulation.

With the introduction of conventional medicine in China in the twentieth century, both the understanding and treatment of RM have made considerable progress. In 1982, Luo Yuankai, an eminent expert in gynecology in TCM, defined the female reproductive axis that governs female reproduction in the context of TCM, which is similar to the hypothalamic-pituitary-ovarian axis in conventional medicine. The female reproductive axis is an improvement of the TCM theory in gynecology and serves as an important guideline for the treatment of RM and other gynecologic diseases. Furthermore, the concept of combining traditional and western medicine has been gradually accepted by many physicians in both TCM and conventional medicine [37-39]. The development of modern medical diagnosis promotes the standardization of TCM [40]. In addition, pharmaceutical companies have developed TCM patent prescriptions, including Zishenyutai Pill by Baiyunshan Zhongyi Pharmaceutical Company of Guangzhou and Gushenantai Pill by Boran Pharmaceutical Company of Beijing. The TCM patent

prescriptions are manufactured in the form of pills and syrup to allow easy preparation and consumption.

Modern researches on RM

Nowadays, the mainstream therapeutic strategy for RM in TCM is divided into two stages: treatment before pregnancy and tocolysis after pregnancy. Treatment before pregnancy lasts for 3 to 6 months depending on the TCM practitioners' judgement. According to the concept of differential diagnosis in TCM, treatment before pregnancy aims at improving the function of the kidney and spleen, followed by detoxification and improvement of blood circulation. After fertilization, tocolysis is performed for the control of the Chong and Ren meridians and is the key to successful therapy. In addition, modern TCM practitioners employ new medical tools and biomarkers, including ultrasonography and human chorionic gonadotropin, for the regular monitoring of fetal development.

In the last two decades, modern pharmacological studies on Chinese herbs for RM have been conducted using single ingredients and whole plants [25-34]. Modern medical research usually focuses on a single drug to avoid confounding factors. However, many active ingredients have synergistic effects when used in combination. Therefore, it is essential to assess the pharmacology, safety, and efficacy of these products considering the entire prescription. These studies have identified the following mechanisms that could explain the therapeutic effects on RM: (1) improvement of the quality of follicles and endometrial receptivity [31], (2) amelioration of luteal function [25], (3) regulation of immune responses [30], (4) improvement of the prethrombotic state [41], (5) upregulation of the expression of the progesterin receptor in the maternal-fetal interface [27-28], and (6) control of hysteromyoma and endometriosis [42-43]. Table 3 lists the major studies (searched from January 1996 to December 2015 in the China National Knowledge Infrastructure database) that have investigated the mechanisms of TCM drugs for RM [25-34]. In addition, some clinical trials evaluated the therapeutic effect of TCM on RM. Yang and colleagues conducted a systematic review of Chinese herbal medicines and found that the administration of medicines such as Shoutai Pill and Antai Decoction increased the live birth rates and improved the embryonic development in women with RM [44]. However, the methodologies on randomization, baseline definition, and sampling were not comprehensive in most of the studies [44, 45].

Conclusion

Because of the complexity and diversity of the herbs used in TCM prescriptions and the lack of quantitative studies, more evidence from properly controlled studies is needed. We believe that this review may trigger future interest in evaluating the pathogenesis and treatment of RM in the context of TCM and may allow the development of systematic pharmacological and clinical studies and a



better evaluation of the therapeutic effects of TCM on RM.

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