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# Research Progress of Chinese Medicine in the Treatment of Recurrent Miscarriage of Unknown Origin

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Abstract: URSA is a form of slippage in Chinese medicine, which causes great psychological and mental stress to patients and seriously affects their lives and physical and mental health. The pathogenesis of URSA is still unclear in Western medicine, and it is mainly treated by various modalities such as immunotherapy, but its efficacy and safety are highly controversial. Chinese medicine, on the other hand, has clear advantages and definite efficacy in the treatment of this disease. Therefore, this paper reviews the research progress of URSA from three major aspects, including the understanding of Chinese medicine, Chinese medicine treatment and mechanism of action, in light of the relevant literature in recent years.

#### 1. Introduction

Recurrent abortion (RSA) is defined as a woman experiencing 2 or more consecutive fetal losses with the same partner. And occurring before 28 weeks of gestation, with a fetal mass of less than 1000g [1]. The incidence of recurrent miscarriage in couples of childbearing age is approximately 3% and the risk of recurrent RSA increases with the number of miscarriages and the age of the woman of childbearing age [1]. Epidemiological studies have shown that the risk of recurrent miscarriage is approximately 29% after 2 consecutive spontaneous abortions, 33% after 3 spontaneous abortions and 42% after 4 spontaneous abortions [2-3]. Currently known causes of RSA include genetic factors, immune factors, endocrine abnormalities, thrombophilia factors, anatomical abnormalities of the reproductive tract, and reproductive tract infections [4], as shown in Table 1. However, up to 50% of RSA cannot be found clinically, that is, the causative factors cannot be detected with current examination techniques, and are known as unexplained recurrent miscarriage [5]. URSA causes great psychological and neurological stress to female patients, seriously affecting their quality of life and social relationship harmony [6]. For RSA with a clear etiology, definitive treatment can be provided to address the cause. Because the pathogenesis of unexplained recurrent miscarriage is still unclear, there are no specific clinical measures to treat and prevent it, so it has become a hot and difficult problem for research in the field of gynaecology.

At present, for unexplained recurrent miscarriage, western medicine mainly focuses on immunotherapy, such as immune cell infusion therapy, LIT and IVIG; anticoagulation therapy, such as aspirin and low-molecular heparin; progestin and glucocorticoids and other drugs, but the above

treatment modalities are mostly small clinical samples, observational and exploratory studies, with certain limitations, and the treatment effect is not large, and its safety and efficacy are yet to be The safety and efficacy of these treatments need to be further confirmed [7]. In recent years, Chinese medicine has used its thinking of "pre-conception conditioning, post-conception preservation and sequential treatment" in combination with evidence-based treatment, which is quite distinctive in the prevention and treatment of unexplained recurrent miscarriage, making Chinese medicine a great advantage in the treatment of unexplained recurrent miscarriage. Therefore, this paper reviews the research progress in three major aspects of Chinese medicine, including the understanding of unexplained recurrent miscarriage, the treatment of Chinese medicine and its mechanism of action.

Table 1: Etiology of Recurrent abortion (RSA)

Etiology	Precise cause	Explaination
	Chromosome abnormality of	Autosomal balanced translocation
Genetic factors	chorionic villi cells	The Robertsonian translocation
	Abnormal chromosome	Aneuploid
	among the spouses	Chimera
Anatomic factors	Abnormality of	
	Gynecological examination,	
	B-ultrasonics, HSG, cervix	
Thrombophilia	Hereditary factor	Pregnancy is in a hypercoagulable state, which
		can easily lead to genetic thromboembolism and
		spontaneous abortion
	APS	APS is a noninflammatory autoimmune disease
		characterized by arterial and venous thrombosis,
		pathological pregnancy (early miscarriage and
		late stillbirth), and thrombocytopenia in clinical
		practice
Infectious factors	TORCH-IgM, UU and CT	
Endocrine factors	Insulin resistance	PCOS, AMH↑
		Poor ovarian response, AMH↓, FSH↑
	Hyperprolactinemia	
	Inyroid dysfunction	Hyperthyroidism during early pregnancy
		Hypothyroidism
	Luteal insufficiency	
Immune factors	Autoimmune related factors	ANA
		Cytokines (interleukin, TNF-a)
	Unclear factors	NK cells
		Anti-HLA antibody
		Anti-sperm antibody
Male factor	Oligoasthenozoospermia	
	Sperm malformation	

# 2. Chinese medicine understanding of unexplained recurrent miscarriage

According to the history and clinical manifestations of this disease, URSA belongs to the category of "counting abortions", "habitual abortion" and "repeated pregnancy and miscarriage" in Chinese medicine.

# 2.1. Ancient medical knowledge

Wang Shuhe of the Western Jin Dynasty mentions the key points related to abortion in his book "Pulse Classic": "If a woman is thirsty in the third month of pregnancy and her pulse is tardy, she wants to be hydrated, and if she has abdominal pain, she must have an abortion". It also mentions that acupuncture is a contraindicated treatment during pregnancy and can easily lead to abortion. Chao Yuanfang of the Sui Dynasty proposed the name of several abortions in his book "Treatise on the Origin of the Diseases" and mentioned kidney deficiency and weakness of qi and blood as its causes. Wu Qian was the first to propose the name "slippery foetus" in The Golden Guide to Medicine, and the pathogenesis of the disease of loss of both the ramifications of the ramifications. In the Qing dynasty, Fu Qingzhu said in his book "Fu Qingzhu Women's Science" that "the foetus is also a result of the interconnection of essence and blood", suggesting that kidney deficiency, deficiency of both qi and blood, lack of intercourse between the heart and kidney, and blood heat could lead to foetal abortion. Wang Qingren of the Qing dynasty said in his book "Correcting Errors in Medicine": "I don't know that in the womb, stagnant blood first occupies the ground ... The blood does not enter the fetus, and the fetus is not nourished by blood, hence the miscarriage", emphasizing that the absence of blood stasis in the uterus prevents the new blood from returning to the menstruum and prevents new pregnancies ... if the blood is deficient ... so the number of falls also". It is also proposed to take Duzhong pill to prevent and control slippage. In the Ming Dynasty, Zhang Jingyue clarified that the onset of the disease is usually in the first three months of pregnancy and in the fifth and seventh months of pregnancy, and proposed that "abortions in miscarriage are often seen in the third trimester and between May and July, and the next abortion is bound to recur as scheduled", and that the etiology and pathogenesis of the disease were discussed in detail in Jing Yue Quan Shu, suggesting that the treatment should be based on deficiency of the liver and spleen, deficiency of qi and blood, disharmony of the liver and spleen, and blood heat. The principle of "pre-cultivating its damage" was emphasized in the treatment. Sun Yikui of the Ming dynasty said in his book "Chishui Xuanzhu": "Whenever the foetus is protected, the spleen and stomach should be taken care of. The spleen and stomach are the bins of the five viscera and six internal organs", indicating that it is particularly important to regulate the spleen and stomach in the protection of the foetus. Wang Kentang believes that blood heat moves the foetus, and that the blood heat is not able to nourish the foetus, which is the main cause of abortion. In the Qing Dynasty, Shen Jin'ao also mentioned in his book "Gynecological Jade Ruler" that "nurturing the foetus is all in the spleen and stomach ... The foetus is easily aborted when the spleen and stomach are injured".

#### 2.2. Modern medical knowledge

Most modern medical practitioners believe that the main etiology of slippage is kidney deficiency, spleen deficiency, qi and blood deficiency and blood heat, but kidney deficiency is the main cause and can be accompanied by blood stasis, phlegm and other pathological products. "Kidney deficiency and deficiency of Qi and Blood, and Blood-Heat, can lead to abortion. "The spleen is the main transporter and the source of qi and blood. The weakness of the spleen and stomach and the lack of qi and blood, or the injury to the spleen from diet or fatigue, or the long-standing illness that depletes qi and blood, leads to deficiency of both qi and blood and the loss of nourishment of the ramus, resulting in repeated pregnancy and abortion and slippage. Zhang Xichen believed that tonifying the kidneys was the key to treating this disease and created "Shou Fetus Pill" to tonify the kidneys, benefit Qi, consolidate the flushing and calm the foetus [8]. Master Xia Guicheng believed that deficiency of the kidney is the root of fetus slippage and that tonifying the kidney is the key to consolidating the fetal element, and should be balanced with nourishing the flushing [9]. Prof. Luo Songping believes that the pathogenesis of URSA is due to the deficiency of the kidney and the damage to the ramus,

and that this type of patient has a long duration of illness, with many cases of mixed deficiency and reality, so the clinical practice should be based on nourishing the kidney and combining it with invigorating blood [10]. Professor Wu Quansheng believes that URSA is closely related to the loss of harmony between Qi and Blood, and therefore the treatment of this disease needs to incorporate the theory of Qi and Blood throughout. The treatment should be tailored to the individual in stages and phases according to the different physiological stages [11]. Professor Zhang Qin believes that deficiency of both spleen and kidney is the key to the pathogenesis of slippage, and most clinical patients are suffering from deficiency of the root and symptoms of the disease, so the kidney should be tonified to cultivate the spleen and at the same time, heat, dampness and stasis should be cleared [12]. Professor Liu Hongqi believes that the basic pathogenesis of URSA is deficiency of both spleen and kidney, deficiency of Qi and blood stasis, resulting in "damage to the ramus and loss of solidity of the fetus", and the clinical evidence should tonify the kidney, strengthen the spleen and benefit Qi, nourish blood and invigorate blood to calm the fetus [13]. Lu Lidan et al. considered that the main evidence of slipped foetus is kidney deficiency with stasis, and the treatment should be to tonify the kidney and invigorate blood, and to strengthen the spleen and remove stasis.

## 3. Chinese medicine in the treatment of recurrent miscarriage of unknown origin

It is the characteristic and advantage of TCM gynaecology to help pregnancy and foetus. It is said in the Su Wen - The Four Qi Regulating Spiritual Discourses that "the sage does not treat the disease before it occurs", indicating that we should prevent the disease before it occurs and not treat it after it has become established, because it is too late to treat it after it has taken shape. It is also stated in the Ge Zhi Yu Lun that "Instead of seeking treatment after a disease has developed, it is better to take care of it before it does. "Therefore, the treatment of RSA should begin at the stage of pregnancy preparation, and be staged before and after pregnancy, so as to prevent the disease before it becomes a disease and to prevent it from becoming a disease.

## 3.1. Pre-conception conditioning

Zhang Jiebin of the Ming dynasty mentioned in his "Jing Yue Quan Shu. The treatment of abortion must be based on the source of nurturing the foetus and pre-cultivating its damage, and the method of preserving the foetus is not derived from this", which indicates that the treatment of URSA should pay attention to pre-conception conditioning.

"Pre-conception intervention" is fundamental to the treatment of RSA, and the importance of "prevention before conception" in the diagnosis and treatment should be emphasized. Some studies [14] have shown that if Chinese medicine conditioning is carried out before pregnancy, it can effectively improve the treatment efficiency. Therefore, it is important to promote the idea of "treating the disease before it occurs" and to provide treatment before the patient becomes pregnant.

It is vital that the husband and wife are in tune with each other. If "the male sperm is not strong and the female sperm is not healthy, the fetus will not be real". In Zhang Zhongjing's "The Essential Guide to the Golden Horoscope" of the Eastern Han Dynasty, it is written that "a man with a weak and astringent pulse is childless and his essence is cold". In the "Jing Yue Quan Shu - Women's Rules", it is suggested that "weak father's qi" causes the fetal element to be unconsolidated. Professor Huang Guangying [15] mentioned in his treatment of abortion, for couples with URSA, even if the male partner's semen routine is not abnormal, the male can also be adjusted. From lifestyle, smoking, alcohol and diet, combined with emotional regulation and medication treatment, this adjustment can make the "male sperm" more "strong". Han Ling [16] showed through clinical observation that the pre-conception intervention of Kidney Strengthening and Fertility Pellets for patients with Kidney Qi Deficiency URSA was safe and effective, and could improve blood HCG levels, promote embryonic

development and increase the success rate of fetal preservation, and its comprehensive effect was significantly better than simple post-conception medication. Li Xiaojun [17] showed through clinical research that preconception intervention treatment with the method of tonifying the kidney and strengthening the spleen could improve the level of Chinese medical evidence in URSA with spleen and kidney deficiency, and after preconception intervention with Chinese medicine could improve the early pregnancy success rate of URSA patients with another pregnancy, improve pregnancy outcome and lay a good foundation for the next pregnancy. In a Meta-analysis, Ren Mengxue [18] showed that preconception intervention with TCM for RSA may have some efficacy advantages in increasing the success rate of pregnancy, i.e. , improving the success rate of pregnancy preservation and live birth, improving coagulation and post-pregnancy sex hormone ( $\beta$ -HCG, P) levels, without serious adverse effects. Professor Liu Hongqi [13] pointed out that women with unexplained recurrent miscarriages should be treated in a sequential and dialectical manner according to their menstrual cycle before conception, so that their bodies can reach a state of balance between yin and yang before trying to conceive.

# 3.2. Post-pregnancy birth control

Although the patient successfully conceived after pre-conception conditioning, repeated pregnancies and abortions in the past have led to repeated damage to the uterus by the golden blade, resulting in a loss of kidney qi, which makes it difficult to consolidate the fetal element and loss of essence and blood, making the fetus displaced. If the herbs are not applied promptly after the pregnancy to strengthen the essence and cultivate the vital energy, it will be difficult for the fetus to ripen. In order to protect the foetus, we should strengthen the spleen, tonify the kidneys, consolidate the flush and calm the foetus. Shou Fetus Pill is composed of four Chinese herbs, namely Cuscuta sinensis, Morinda citrifolia, Radix et Rhizoma ginseng and Agaricus blazei. Cao Qi et al[19] found through data mining that Cuscuta sinensis, Sambucus mulberry, Radix Aconiti and Atractylodes macrocephala were used more frequently in post-pregnancy interventions for recurrent miscarriage, and the main meridians were the liver, kidney and spleen meridians. Guo Hongyu [20] et al. demonstrated through clinical studies the advantages of the formula for benefiting the kidney and resolving blood stasis in improving pregnancy rates and increasing the rate of continued pregnancy. Han Chunyan [21] demonstrated through clinical research that tonifying the kidneys and tranquilising the foetus can improve the endocrine hormone levels of URSA patients with kidney deficiency, and has significant efficacy and low incidence of adverse reactions in URSA with kidney deficiency. Chen Yasong [22] randomly divided 112 URSA patients into a combined group and a control group, in which the control group was treated with dydrogesterone, and the combined group was treated with Taishan Panshan on the basis of the control group, and the results showed that the levels of oestradiol, human chorionic gonadotropin, and luteinizing hormone in the combined group at the twelfth week of gestation were significantly higher than that in the control group. Lu Lidan et al. showed through clinical observation that the combination of tonifying kidney and activating blood formula with conventional western medicine in the treatment of patients with unexplained recurrent miscarriage with kidney deficiency and stasis could alleviate patients' clinical symptoms, improve patients' estrogen and progesterone levels, increase the success rate of fetal preservation and regulate immune balance with good safety [23]. Li Yuqing [24] randomly divided 70 patients into the observation group and the control group, with the control group given progesterone treatment and the observation group given Shou Fetal Pill combined with Siwu Tang plus reduction treatment. The results showed that the overall efficiency and pregnancy success rate of patients in the observation group were higher than those in the control group.

## 3.3. Sequential therapy

According to Zhao Wei [25], a patient who has had several abortions has a deficient uterus, which is like a poor soil that cannot provide good nutrition for the seed to grow. If one wants to avoid the recurrence of abortion, one should not rush to seek a child, but should carry out sequential treatment, conditioning the body before conception so that the uterus can recover before conception, and timely preservation of the fetus after conception. Wan Zhongyan et al [26] used the random number table method to divide 120 patients with URSA into a control group and a treatment group. The control group was not given Shoufei Pills before pregnancy, and the post-pregnancy routine fertility preservation treatment (progesterone injection + VE capsule + enoxaparin injection), while the treatment group was given Shoufei Pills orally for 2 months before pregnancy, and continued to take Shoufei Pills orally for fertility preservation treatment after pregnancy on the basis of the routine treatment in the control group. The results showed that the success rate of fetal preservation was higher in the treatment group than in the control group, and the incidence of adverse reactions was comparable between the two groups. Zhu Yunpu et al [27] randomly divided 97 patients with URSA into a control group and a treatment group. In the treatment group, oral Chinese medicine was used for 3 menstrual cycles before pregnancy and oral fetus preservation treatment was given after pregnancy using Xia Lao's "tonifying the kidney and regulating the circumference therapy". In the control group, only post-pregnancy fetal preservation treatment was given as in the treatment group. The results showed that the cure rate of the treatment group was significantly higher than that of the control group. He Wanting [28] randomly divided 112 patients with URSA into the observation group and the control group. The observation group was treated with "tonifying the kidney and regulating the perinatal cycle" before pregnancy, and was given oral fetal preservation treatment with antifetus combination for 3 months after pregnancy, while the control group was only given oral fetal preservation treatment with antifetus combination for 3 months after pregnancy. The results showed that after the treatment, the observation group showed a more significant reduction in the evidence score than the control group. The β-HCG levels in the observation group were higher than those in the control group at all times of pregnancy. The treatment efficiency of the observation group was higher than that of the control group. All these indicate that the combination of pre-conception and post-conception antirefetal sequential treatment of URSA can increase the clinical live birth rate and is worthy of clinical application.

### 4. Mechanism of action studies

Chinese medicine has a wide range of targets, pathways and complex mechanisms of action. Modern pharmacology suggests that the flavonoids in Cuscuta can improve progesterone and inhibit the synthesis of inflammatory factors to stabilize Th1 and Th2 levels and enhance the patient's immune system; the tanshinones in Salvia can promote blood rheology and prevent the appearance of thrombotic precursors; the alkaloids in Radix et Rhizoma can inhibit uterine smooth muscle contraction; and the polysaccharides in Colla Corii Asini can enhance the body's bone marrow haematopoietic capacity [29]. Polysaccharide compounds can enhance the bone marrow haematopoietic capacity of the body [29]. Studies have shown that kidney tonic herbs can increase the estrogen content in the uterine cavity, thus improving endometrial tolerance. Related studies have reported that the active ingredients of Morinda citrifolia and the aqueous extract of Cuscuta sinensis have the effect of promoting the secretion of progesterone and estradiol and reducing the rate of stillbirth [30]. Han Cong[31] showed through a network pharmacological analysis that oral administration of tonifying kidney and solid punch soup before pregnancy in clinical URSA patients could improve URSA by anti-inflammatory, regulating immune balance and modulating blood status, with multiple targets and pathways. feng et al[32] showed through a clinical trial that tonifying kidney

and activating blood formula might achieve the effect of improving URSA by increasing serum PP14 levels in non-pregnant women while decreasing the expression of IL-17 and IL-23. improve the effect of URSA. Jiang Sha et al[33] showed that post-pregnancy treatment of URSA patients with the tonifying kidney and invigorating blood method could significantly increase the serum P level, reduce the secretion of inflammatory factors in the maternal-fetal interfacial plane and adjust the maternal-fetal immune balance, thus increasing the success rate of fetal preservation and late neonatal live birth rate.

## 5. Summary

In recent years, the incidence of URSA has been on the rise due to increased work pressure and changes in lifestyle. Most patients with URSA cannot be treated clinically according to the cause of the disease because the cause is unknown. Most patients with URSA cannot be treated clinically according to the cause of the disease as the cause is unknown. Western medicine mainly treats the disease through various modalities such as immunotherapy, but its efficacy and safety are highly controversial, making the treatment of URSA a difficult problem in the field of reproductive medicine today.

Chinese medicine has clear advantages and definite efficacy in the treatment of this disease. Compared to Western medicine, TCM treatment has fewer adverse effects and can compensate for the lack of Western medicine while curing the disease. However, due to the complex pathogenesis of URSA, there are currently fewer reports on the treatment of this disease with Chinese medicine. Therefore, more systematic and in-depth research should be conducted on the rules of Chinese medicine and its mechanisms of action to prevent and treat the occurrence of URSA, improve the success rate of fertility preservation and safeguard women's reproductive health.

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