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Review

Evidence-based interventions of threatened miscarriage

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ABSTRACT

Threatened miscarriage is the commonest complication of early pregnancy and affects about 20% of pregnancies. It presents with vaginal bleeding with or without abdominal cramps. Increasing age of women, smoking, obesity or polycystic ovary syndrome (PCOS) and a previous history of miscarriage are risk factors for threatened miscarriage. The pathophysiology has been associated with changes in levels of cytokines or maternal immune dysfunction. Clinical history and examination, maternal serum biochemistry and ultrasound findings are important to determine the treatment options and provide valuable information for the prognosis. Bed rest is the commonest advice, but there is little evidence of its value. Other options include progesterone, human chorionic gonadotropin (HCG) and muscle relaxants. The complementary and alternative medicine (CAM) therapies such as acupuncture and Chinese herbs have also been tried. There is some evidence from clinical studies indicating that CAM therapies may reduce the rate of miscarriage, but the quality of studies is poor. Thus, further double-blind, randomized-controlled trials are necessary to confirm its effectiveness, especially acupuncture and Chinese herbs.

Key words: Threatened miscarriage, Evidence-based, Intervention, Complementary and alternative medicine
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Introduction

Threatened miscarriage is the commonest complication of early pregnancy and is often associated with anxiety and stress regarding the pregnancy outcome. It occurs in about 20% of recognized pregnancies and about half of these will eventually suffer an actual miscarriage[1-4]. These women usually present vaginal bleeding, with or without abdominal pain and cramps, but the cervix is closed. Bleeding during pregnancy can cause maternal anxiety and emerging evidence suggests that it may be associated with poor fetal and maternal outcomes[2, 5]. Furthermore, there is an increased risk of subsequent pregnancy complications, such as Antepartum haemorrhage (APH), premature rupture of membranes (PROM), intrauterine growth retardation (IUGR) and preterm delivery after a threatened miscarriage[6-8].

Risk of threatened miscarriage is increased in older women and those with a previous history of miscarriage. For example, in a study of 182 women with threatened miscarriage, the miscarriage rates between age of women 31~40, 16~20 and 21~30 years were 27.1%, 18.2 and 7.1%, respectively[9]. Other factors that contribute to an increased risk include endocrine abnormalities[10] (such as diabetes, PCOS or thyroid dysfunction) and poor life or working environment[11-13].

A number of treatment options are available, including bed rest and a simple wait and watch policy, and treatment with progesterone or HCG, as well as using uterine muscle relaxant drugs. Unfortunately, these western medicines have some adverse effects. Nausea, headache and sleepiness are common, and high doses may result in drowsiness and liver toxicity. For instance, oral administration of progesterone shows several disadvantages including the extreme variability in the plasma concentrations obtained and poor bioavailability. Vaginal administration of progesterone is inconvenient for women with vaginal bleeding, and the absorption is also unreliable[14]. As another option to preserve pregnancy, CAM therapies include acupuncture and Chinese herbs have the superiority of little side effects compared with Western medicine. Within fertility research, acupuncture demonstrated beneficial hormonal responses with decreased miscarriage rates and promoted specific beneficial effects in terms of positive emotion and hormonal responses in early pregnancy[15]. Chinese herbs made up of products from plants mostly and some animal and mineral substances have become very popular and are commonly used as an alternative treatment for threatened miscarriage recently[16]. So, it is worthwhile to examine the possible treatment benefits of CAM therapies for miscarriage. The aim of this manuscript is therefore to summarize the current knowledge in the threatened miscarriage and to analyze the most updated research and clinical usage, mechanism and side-effects of CAM therapies for threatened miscarriage, in order to guide future researches and clinical applications.

Clinical presentation

Threatened miscarriage is the commonest complication in the first half of pregnancy, which is a term, used when a woman who is pregnant less than 20 weeks with a live fetus experiences vaginal bleeding and abdominal pain, but the cervix is closed. Vaginal bleeding during early gestation occurs in 20% to 25%

pregnancies and may last for days or weeks[17]. The subject's perception about the amount of bleeding, compared with her normal menstrual period, is important in predicting a failed pregnancy. In general, the greater amount of perceived blood loss, the greater chance of a non-viable pregnancy may have. Threatened miscarriage rarely presents with heavy vaginal bleeding. For abdominal pain, patients may or may not report pain that is similar to periodic pain or cramps. This is due to the contraction of the uterus in response to irritation caused by the bleeding[18]. On vaginal examination, the cervical os is closed and no cervical motion tenderness is found. Diffuse uterine tenderness and/or adnexal tenderness may be present[19]. Anxiety and stress considerably increased the risk of miscarriage up to 2.6 times. And these psychological symptoms could persist for 6 months to 1 year after the miscarriage[20-22]. Up to 17% of women with threatened miscarriage have pregnancy complications later, such as placental abruption, unexplained APH, PROM, IUGR and preterm delivery or pre-eclampsia[6-8].

Differential diagnosis in women with early pregnancy per vaginal bleeding is outlined in the flow chart in Figure 1[23]. The process also involves the differences between threatened miscarriage and other miscarriages contributing to differential diagnosis and treatment through history taking, pelvic examination and the checking of vital signs.

1. Pathophysiology

The pathophysiology of threatened miscarriage is still not understood. Currently the known pathogenesis of threatened miscarriage includes changes in levels of cytokines and placental membranes, maternal immune dysfunction, and endocrine abnormalities. Most women with threatened abortion probably have multiple risk factors for miscarriage.

1.1 Abnormal cytokines profiles

The pathophysiology of threatened miscarriage in terms of cytokines involves a change in the T helper (Th) 1/Th2 balance resulting from an increase of uterine Th1 type proinflammatory cytokines and/or a deficiency of Th2/3 type cytokines, therein increased maternal serum interleukin (IL)-2 receptor and tumor necrosis factor (TNF)-α levels[24-26]. And a pilot study of women with threatened miscarriage showed that plasma anandamide level was associated with presence or absence of subsequent miscarriage. The endocannabinoid anandamide(N-arachidonoyl-ethanolamine), a non-charged endogenous cannabinoid neurotransmitter, is critical for both the endometrium in preparation for implantation and the synchronous development of the blastocyst. High anandamide levels are not essential for successful implantation[27]. Changes in levels of these cytokines could help to predict the outcome and thus prevent complications.

1.2 Immunologic dysfunction

Immunologic recognition of pregnancy is crucial to the maintenance of gestation. And inadequate recognition of fetal antigens may cause abortion[28]. Regards to threatened miscarriage, studies show that the presence of anti-b2-glycoprotein I antibodies is associated with an increased risk of pregnancy loss in women with threatened miscarriage in the first trimester[29]. Evidence suggests that circulating levels of chemokines which are proteins involve in regulation of inflammation and immune response are associated with increased risk of miscarriage and may have a regulatory function in pregnancy. Elevated epithelial cell-derived neutrophil-activating protein-78 (ENA-78) levels, a protein involved in regulation of angiogenesis and leukocyte recruitment, are associated with increased risk of miscarriage as the collection-outcome increased interval[30]. Because according to the importance of angiogenesis in placentation and fetal development, ENA-78 may regulates vascularization in normal pregnancy. While higher ENA-78 may reflect an underlying condition giving rise to the need for increased angiogenesis[30].

1.3 Oxidative stress

Lipid peroxidation and alterations in antioxidant enzyme activities may be of importance in the pathogenesis of miscarriage. The architecture of the human first trimester gestational sac limits fetal exposure to oxygen (O_2)[31]. Placenta and fetus develop in a physiologically low O_2 environment and their metabolisms are essentially anaerobic. O_2 free radicals are generated under hypoxic conditions and confirmed to be a potential teratogenic threat to the fetal tissues and are known to be related to the pathophysiology of common human pregnancy disorders, including miscarriage. Oxidative stress in placenta tissues of early pregnancy failure is a characteristic in miscarriage, although activation of antioxidant enzymes, such as catalase (CAT) and glutathione peroxidase (GSH-Px) developed a compensatory mechanism against possible oxidative damage[32,33].

Besides, a modified nitric oxide (NO) pathway might play an important role in the physiological changes of advancing gestation but may also contribute to the pathophysiology of miscarriage. A study showed that serum NO levels clearly decreased compared with non-pregnant patients and patients with regular pregnancy and threatened abortion. The data report implied that a direct functional role of the NO mediator in early embryonic development confirmed its importance in the uterus and cervix during abortion[34]. Therefore, any factors balancing NO metabolism might be useful in the treatment of miscarriage, reducing the substantial morbidity and associated mortality.

1.4 Endocrine disorders

For most other miscarriages, the causes are unknown, but some may be related to endocrine disorders of mothers. The most common endocrinologic factors are polycystic ovarian syndrome (PCOS) and obesity. Several factors have been implicated as potential contributors to miscarriage in PCOS. In addition to fetal defects, these include anatomically polycystic ovaries, obesity, endometrial defects, placental thrombosis, and hormonal abnormalities such as insulin resistance or excess androgen secretion. Notably, insulin resistance has been linked to several of the aforementioned contributors to pregnancy lost[35]. A prospective study of

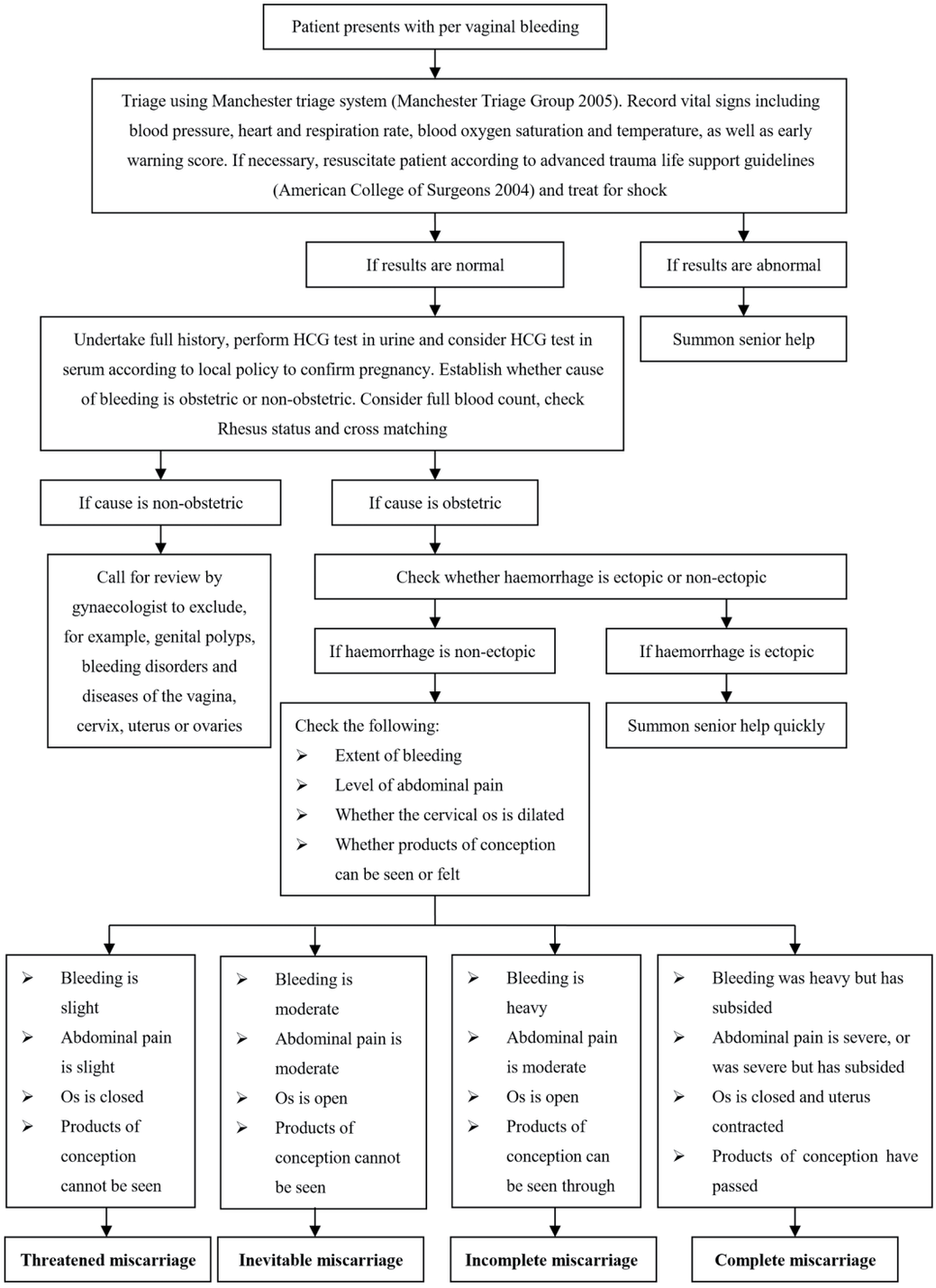

Figure 1. Flow chart for diagnosing women with early pregnancy per vaginal bleeding[23] (Marquardt U., 2011).

separately stepwise logistic regression analyses found that the plasminogen activator inhibitor activity was a positive independent and reversible risk factor for miscarriage in women with PCOS. Furthermore, another review suggested that the hyperinsulinemia is a -characteristics of patients with PCOS, might lead to a decrease in the receptivity of the uterus for implantation. Hyperinsulinemia has also been shown to be associated with increased levels of plasminogen activator inhibitor-1, a powerful inhibitor of fibrinolysis, as a potential factor involved in pregnancy loss. Thus it may be indirectly linked to miscarriage[36, 37].

In addition, obesity will cause increased risks of congenital anomalies, preeclampsia, gestational diabetes, and stillbirth[38-40]. There are also data suggesting the risk of miscarriage is increased among obese women[41]. The conceivable mechanisms may be effects of obesity on the oocyte or embryo could affect the embryo's potential for development. It is possible that obesity imparts a negative influence on the

endometrium influenced by the hormones including insulin and adipokines such as leptin and adiponectin, which together increase the risk of miscarriage[42-45].

1.5 Placental membranes

Combining ultrasound and in-vitro experiments have indicated that the maternal circulation inside the placenta is associated with a physiological oxidative stress which can be the trigger for the formation of the placental membranes[46]. And there is clear ultrasound evidence for excessive entry of maternal blood inside the intervillous space having a direct mechanical effect on the villous tissue, and an indirect oxidative stress effect that contributes to cellular dysfunction and/or damage[47]. The abnormal development of these membranes can lead to subchorionic hemorrhage which may result in placental separation and threatened miscarriage[48]. Additionally, the presence of a hematoma may also be associated with a chronic inflammatory reaction in the decidua, resulting in persistent myometrial activity and expulsion of the pregnancy[49].

2. Risk factors

Risk factors include environment of living and work, maternal age, endocrine, a history of miscarriage, paternal age and others (Table 1). The identification of these risk factors and development of an interaction model of these factors will help clinicians to recognize pregnant women who require extra monitoring and who may benefit from therapeutic interventions, especially during the first week of pregnancy, to prevent a miscarriage[50][53].

Numerous researches have examined the association of miscarriage with some diet, behavior or lifestyle and work environment. Poor dietary intake of vitamins has been confirmed with the association of miscarriage. Supplementing women with vitamins either prior to or in early pregnancy may reduce the risk of miscarriage, but recent review cannot confirm its efficacy. However, taking vitamin supplements before or at the time of conception may more likely lead to a multiple pregnancy. The impact of different combinations of vitamins needs to be further studied[54]. In addition, it has been shown that caffeine consumption > 300 mg/day may double the risk of miscarriage[55]. Whereas, there was no evidence that daily consumption of 400 μg of folic acid before and during early pregnancy influenced the risk of miscarriage[56]. Besides, a slightly increased risk was found for dental workers exposed to mercury amalgam, some acrylate compounds, solvents and disinfectants[57].

It is well known that miscarriage risk increases with age of women. Because there is a high risk of pre-gestational, gestational complications and perinatal loss, pregnancy at 40 and over is a high-risk pregnancy[58]. And high maternal age was a significant risk factor for spontaneous miscarriage irrespective of the number of previous miscarriages and parity. The risk of spontaneous miscarriage was 8.9% in women aged 20-24 years and rose to 74.7% in those aged 45 years and older (Table 2)[59, 60]. The increased risk was much greater in couples with a woman aged 35 years or more and a man aged 40 years or more[61]. In another cohort, the risk of miscarriage was found significantly increased in women at higher age (>33 years), lower body mass index (≤20 kg/m^2) and lower serum progesterone concentrations (≤12 ng/ml) prior to the onset of the miscarriage[50]. And in a Danish National Birth Cohort, the researchers found that pregnancies fathered by a man aged 50 or more years had almost twice the risk of fetal loss compared with pregnancies with younger fathers. Even adjusting the potential residual confounding of the relation by maternal age, the result was the same. And the paternal age-related risk of late fetal death was higher than the risk of early fetal death which started to increase from the age of 45 years[62]. Besides, the incidence of fetal loss decreased with gestational age (Table 3)[63].

An association between endocrine and metabolic diseases and miscarriage has been demonstrated in several studies. Such as obesity, which has been linked to a number of adverse

Table 1. The common risk factors for miscarriage.

Category	Risk factors
Demographics & history	Advancing maternal age>35 or paternal age>45
	Previous miscarriage(s)
	The incidence of vaginal bleeding
	Poorly controlled endocrine and metabolic diseases
	Dietary factors e.g. caffeine consumption
	Consumption of drugs
	Pre-pregnancy BMI: Being underweight
	Behavioural factors and occupational exposure/ education
Ultrasound findings	Discrepancy between gestational age and crown to rump length
	Discrepancy between menstrual and sonographic age of > 1 weeks
	No foetal heart activity
	Foetal bradycardia < 120/min
	Empty gestational sac > 15-17 mm diameter
	Gestational sac ≥ 13 mm diameter
	Without yolk sac
	Subchorionic haematoma

Table 2. Miscarriage rates stratified by maternal age at conception[60].

Age(years)	Total number of pregnancies	Miscarriage rate
20-24	350395	9%
25-29	414149	11%
30-34	235049	15%
35-39	93940	25%
40-44	25132	51%
≥ 45	1865	75%

Table 3. Relationship between gestational age and subsequent fetal loss rate in a series of 668 unselected pregnancies undergoing routine first-trimester transvaginal sonography[63].

Gestation (weeks)	Risk of miscarriage (%)
6	10.3%
7	7.9%
8	7.4%
9	3.1%

reproductive outcomes, is an increased risk of miscarriage regardless of the method of conception[64]. A mild increase in the body mass index does not increase the risk of miscarriage, whereas obese and underweight patients have a small but significant increased risk of miscarriage in the subsequent pregnancy[64, 65]. And hormonally substituted frozen-thawed embryo (FET) is associated with an even higher miscarriage rate[66]. In a cohort of pregnant women without overt thyroid dysfunction, the risk of child loss increased with higher levels of maternal thyroid stimulating hormone (TSH). However, maternal free thyroxine (FT4) concentrations and child loss were not associated[67]. The reasons may be maternal immune response, trophoblast function, and maternal thyroid functions are somehow correlated. And the presence of low concentrations of HCG and FT4 and high levels of TSH and gamma globulins in women with threatened abortion suggests a negative outcome for the pregnancy[68].

3. Treatment for threatened miscarriage

A number of treatment options are available. Clinical history and examination, maternal serum biochemistry and ultrasound findings are important to determine the potential treatment options and may help the prognosis. Bed rest is the commonest advice, but there is little evidence of its value. Other options include progesterone, HCG and muscle relaxant. And traditional Chinese medicines including acupuncture and herbs have been tried.

3.1 Bed rest

According to researches, in cases of threatened abortion with or without the presence of subchorionic hematoma, prognostic outcome is better following the treatments with bed rest, uterine sedatives, folic acid supplementation and hormonal treatment[6, 69]. However, the results of another study evaluating the effect of bed rest during pregnancy to prevent miscarriage were different. There were no differences in the risk of miscarriage in the bed rest group versus the no bed rest group and the bed rest in hospital versus the bed rest at home[70]. And there was a higher risk of miscarriage in the bed rest group than HCG therapy group with no bed rest[70]. In conclusion, a large prospective randomized study is required to confirm whether bed-rest has a real therapeutic effect. It must be pointed out to the patients that there was no good evidence indicating that bed rest influenced the outcome. Otherwise the pregnant women may be to blame if they cannot or does not rest and subsequently miscarries[71].

3.2 HCG

Endogenous HCG which is a hormone secreted by the syncytiotrophoblast of the placenta promotes the corpus luteum to secrete progesterone and stimulates early fetoplacental endocrine functions. It is known to play an important physiological role in maintaining the pregnancy. Hence there has been much interest in the use of HCG for treating threatened miscarriage with the aim of preserving the pregnancy. HCG therapy appears to be a logical approach when an endocrine abnormality is suspected. A meta-analysis[72] showed that there was no significant difference in the incidence of miscarriage between HCG and "no HCG" (placebo or no treatment) groups. And when HCG and bed rest alone were compared, there was a significant reduction in the risk of miscarriage. There was no report on adverse effects of HCG on the mother or baby. However, this result should be interpreted with caution, as one trial from which this result is derived was of poor methodological quality. Thus, more good-quality researches are urgently needed to assess the impact of HCG on miscarriage[72, 73].

3.3 Progesterone

Progesterone is an essential hormone in the process of reproduction, which is needed for preparing the endometrium for implantation, and for decidual transformation after implantation. Further, it plays a role in controlling myometrial contractility, and via its immuno-modulating property regulates the feto-maternal immunological relationship throughout pregnancy[74]. Studies have confirmed that progesterone is effective when continuation of pregnancy is hampered by inadequate luteal function, immunological factors, neuroendocrine deficiencies and myometrial hyper-contractility[75]. However, the results about the use of progesterone in recurrent miscarriage for inadequate luteal function are more controversial[76]. Therefore, it is involved in the menstrual cycle and implantation, and is essential for pregnancy maintenance, and so it is thought to be a possible treatment for threatened miscarriage. Another recent meta-analysis found a reduction in the rate of miscarriage with the use of progesterone compared to placebo or no treatment (risk ratio (RR) 0.53; 95% confidence interval (CI) 0.35 to 0.79), suggesting that the use of progesterone is effective in the treatment of threatened miscarriage[77]. Although progesterone is now available commercially and its pharmacokinetics and pharmacodynamics have been well studied, the pathophysiology in pregnancy remains in controversy. Only high dose of progesterone exerts a preventive role against miscarriage in early pregnancy[78].

One of these concerns is the administration route of the hormone. Progesterone can be administered in three ways: orally, vaginally and intramuscularly. Oral administration guarantees optimal compliance by patients, according to patient weight, the optimal dose suggested being between 100 and 200 mg/day, which also shows several disadvantages. The main one is its extreme variability in the plasma concentrations obtained because of individual variability in gastric filling and enterohepatic cycle. The side effects also include nausea, headache and sleepiness. And unfortunately, the bioavailability of oral micronized progesterone is poor and the high doses that are therefore required may induce side effects such as drowsiness and liver toxicity. The vaginal administration induces higher concentrations in the uterus and results in a shift in the concentration of cytokines in endocervical secretions, such as a significant decrease in IFNγ and increase in IL-10 in endocervical fluid[14]. However, it does not result in high and constant blood levels, and the absorption is also unreliable in case of bleeding. Furthermore, the vaginal

route is inconvenient for women with vaginal bleeding, particularly in those with heavy bleeding[79]. And the progesterone administered intramuscularly occasionally results in non-septic abscesses, but it is the only way which achieves optimal blood levels[78, 80]. A study demonstrated that vaginal progesterone administration, but not oral dydrogesterone treatment, resulted in the decrease in the spiral artery pulsatility and resistance index and systolic/diastolic ratio. And insignificant decrease in pulsatility index and resistance index of the uterine artery was observed at 9 weeks and was not associated with the method of treatment. Vaginal progesterone and oral dydrogesterone supplementation have a different influence on the uteroplacental circulation in early pregnancy which is complicated by threatened miscarriage[81].

The mechanisms by which progesterone contribute to the maintenance of pregnancy mainly contain endocrine effects and immuno-modulating role. Activation of progesterone receptors on lymphocytes induces a 35 kDa protein's synthesis which is known as the progesterone-induced blocking factor (PIBF). PIBF results in asymmetric antibodies, T-helper 2 dominance and reduces natural killer cell activity, therefore ensuring protective immuno-modulation[82, 83]. Several studies have also confirmed that besides blocking mitogen stimulated lymphocyte proliferation, progesterone could prolongs allograft survival, decreases the oxidative burst of monocytes, modulates antibody production, reduces the production of proinflammatory cytokines by macrophages in response to bacterial products, alters cytokine secretion of T-cell clones to favor IL-10 production, and inhibits apoptosis by down-regulating Fas, Fas ligand, caspase-8, caspase-3 and polymerase expression as well as up-regulating Bcl-2 expression in the human trophoblast-derived HTR-8/SV neo cells which progesterone receptor exists in[84, 85]. Further, the hormone enhances uterine quiescence and suppresses uterine contractions.

Consequently, although there is a rationale for a protective effect of progesterone by the mechanisms (tocolytic effect, immunological effects and hormonal support), based on scarce data from four methodologically poor trials with 421 women, the existing data cannot support the routine use of progesterone for the treatment of threatened miscarriage. Information about potential harms to the mother or child, or both, with the use of progesterone is insufficient[77,86]. A recent study found that maternal intake of progesterone in early pregnancy is associated with an increased risk of hypospadia in the male offspring[87]. And even if a possible teratology role has certainly been reduced, it cannot be excluded completely yet. Moreover a high incidence of respiratory problems has been noticed in newborns from the patients treated with progesterone, compared with control groups. Another concern is the optimal dose, route, timing of progesterone supplementation, and the different dosages and populations studied[76]. Thus, to obtain a definitive conclusion about progesterone therapy's real effectiveness of threatened miscarriage, and to investigate potential harms as well as benefits, it is necessary to carry out larger, randomized controlled prospected trials.

3.4 Muscle relaxants

Uterine muscle relaxant drugs have been used for threatened miscarriage in an attempt to relax uterine muscle, and thus reduce the risk of miscarriage. There was only one poor quality trial with 170 women studying beta agonist, one of the uterine relaxant drugs, to prevent miscarriage compared to placebo. The result demonstrated that a lower risk of intrauterine death (miscarriage and stillbirth) in the beta agonist group (average risk ratio (RR) 0.25, 95% confidence interval (CI) 0.12 to 0.51), but no difference in preterm birth. Overall, there has been not enough evidence to say if drugs relaxing the muscles of the uterus can prevent threatened miscarriage[88]. More researches on the effect of uterine muscle relaxant drugs on the treatment of threatened miscarriage are needed.

3.5 Acupuncture

As a complement or alternative to conventional therapies, acupuncture is an integral part of traditional Chinese medicine which dates back to 3000–5000 years ago. Using acupuncture treatment on the reproductive endocrinology and infertility has gained increased popularity worldwide. For women presenting with threatened miscarriage, it is known that 50% ~70% of women miscarriage is because of chromosomal abnormalities, but it is unknown what percentage of the remaining women miscarry for unidentified reasons could be aided by therapeutic interventions such as supportive care and acupuncture to maintain a successful pregnancy. However, there is as yet no convincing evidence based on literature that acupuncture is an effective treatment for threatened miscarriage. The only reported study comparing different styles of acupuncture with no attempt to evaluate the acupuncture treatment against a control group was conducted in China[89]. The methodology of this study was poor with a high risk of bias, thus giving no confidence in the reported conclusions. The acupoints were based on the individual characteristics, such as bladder (BL) 23, governor vessel (GV) 4, spleen (SP) 10, SP 6, liver (LR) 3, and kidney (KI) 3[89]. A study [90] reported that 34 women undergoing vitro fertilization-embryo transfer treatment received acupuncture treatment and found a significant reduction in miscarriage rates among the women receiving acupuncture treatment. To further investigate whether acupuncture has the potential to promote beneficial hormonal responses in early pregnancy complicated with threatened miscarriage, a mixed methods study is currently being conducted in New Zealand. In order to exclude other specific therapeutic factors contributing to treatment effects, the randomized controlled trial compares acupuncture treatment to an active control group receiving supportive care only. Moreover, concerning the qualitative aim of this study, thematic analysis will be used to examine the experience of receiving both supportive care and acupuncture[91].

According to the principles of TCM, the mechanisms of acupuncture may stimulate an energetic response involving *qi*[15], correct any imbalances in the flow of life force along meridians and thus cure the diseases when needles inserted into specific body points. From a physiological perspective, acupuncture can not only inhibit the uterine contraction,

but also increase the uterine blood flow[92]. Acupoints on the abdomen are suggested not to be used and some acupoints on the waist such as spleen (SP) 6, large intestine (LI) 4, and conception vessel (CV)1 have to be used with caution as stated in some textbooks.

3.6 *Chinese herbs*

Chinese herbs, as a part of Traditional Chinese Medicines, have been developed and widely used in Asian countries for centuries. Chuang et al[93]. conducted an interview with the 2048 postpartum women from the Taiwan national birth register using structured questionnaires to explore the usage of Chinese herbal medicines in pregnant women. The results of the survey showed that 24.1% women used at least 1 Chinese herb during pregnancy and those with threatened miscarriage used more Chinese herbal medicines than others. Another investigation in the Chinese mainland showed 90.4% (132 of 146) of women having vaginal spotting or bleeding in the first trimester used herbal medicine during pregnancy , including 87.0 % (127 of 146) with threatened miscarriage[94]. The commonest prescription is "An Tai Wan (Quiet Fetus Pill)" or "An Tai Yin (Quiet Fetus Drink)". Active ingredients include Radix Angelicae, Paeoniae Lactiflorae Radix, Radix Scutellariae, Largehead Atractylodes Rhizome, Szechuan Lovage Rhizome and others.

There was a systematic evaluation of the effectiveness of Chinese herbs for threatened miscarriage, which included 44 randomized clinical trials with 5100 participants, all from China, and did not use placebo or bed rest as a control[95]. Twenty trials used Shou Tai Pill, which was a common prescription, while the remaining trials used other formulae. And the controlled western medicines included salbutamol, magnesium sulfate, HCG or progesterone, vitamin E and folic acid.

Five studies followed up the patients until after 28 weeks of gestation and delivery, and the other 39 studies observed the immediate effectiveness. Many of the trials did not report on side effects during the treatments or continuing pregnancy. The classical prescriptions were slightly modified depending on the individual clinical presentations. The results confirmed that the rate of effectiveness (continuation of pregnancy after 28 weeks of gestation) was significantly different between combined Chinese herbal and Western medicines (RR 1.28; 95% CI 1.18 to 1.38; five trials, 550 women). However, the Chinese herbal medicines alone group were not more effective than Western medicines alone to continue the pregnancy beyond and 28 weeks of gestation (RR 1.23; 95% CI 0.96 to 1.57; one trial, 60 women). However, the methodological quality of all the trials was poor. In conclusion, there is not enough evidence from randomized controlled trials on the effectiveness of Chinese herbs for the treatment of threatened miscarriage and to determine if Chinese herbs alone are more beneficial than Western medicines alone for threatened miscarriage.

A review to identify the safety and the adverse events of Chinese herbs used for threatened miscarriage analyzed 32 articles, including 9 RCT, 1 quasi-RCT and 2 controlled trials comparing TCM alone or combined medicines with pharmaceuticals and 20 case series with no controls. The results were dry mouth, constipation and insomnia (2–10%) and intervention failure (3.1–22.3%), diabetic complications (3%), preterm delivery (5%) and neurodevelopmental morbidity (1.8%) were recorded In RCT. And the meta-analysis demonstrated that intervention failure was significantly lower in the combined Chinese medicines groups than in the Western medicines controls (RR= 0.46; 95% CI: 0.30–0.70). There were no difference in adverse effects and toxicity or adverse pregnancy and perinatal outcomes[96]. Moreover, through orally administering pregnant mice, rats and rabbits with Largehead Atractylodes Rhizome (LAR) extracts in various doses (from 1×, 2×, 3× and up to 6× clinical doses) at different gestational periods, Li et al found there were no significant adverse effects in rats and rabbits although fetal resorption, hydrops fetalis and short ear were identified. And the exposure of early LAR increased the incidence of fetal growth parameters and post-implantation loss; late LAR included in gestational duration, prenatal and post-natal mortality. At high clinical doses, congenital skeletal malformations were recorded. This confirmed potential reproductive toxicity of LAR in pregnant animals was identified within the clinical dose[97]. Because LAR may affect limb development by suppressing the expression of limb developmental genes and disturbing programmed cell death during limb formation in mice[98]. Thus, caution should be taken in clinical applications of some herbs like LAR during pregnancy, but most of Chinese herbs are relatively safe in treatment of threatened miscarriage.

The mechanisms of Chinese herbs mainly included inhibiting the secretion of Th1 cytokines, promoting the secretion of Th2 cytokines, and improving the pathological shift of the Th1/Th2 balance[99]. The other possible mechanism was regulating maternal-fetal neuroendocrine and endocrine function by descending the plasma concentrations of β–endorphin (β–EP) which might play a major role in regulating placental function, and raising gonadotrophin releasing hormone (GnRH), HCG, and P[100]. And Chinese herbs should only be administered to pregnant women after a careful benefit-risk assessment, such as some Chinese herbs of heavy-toxicity, promoting blood circulation, relieving stagnant Qi, and purgation which may lead to fetal abnormality and miscarriage are not chosen in the textbooks.

Conclusion

Women presenting with threatened miscarriage are at an increased risk of adverse pregnancy outcomes and under great psychological stress. Clinical history and examination, serum biochemistry of pregnant women and ultrasound findings are important to determine the treatment options and valuable information for the prognosis. Bed rest, HCG and muscle relaxant have not been shown to be effective in threatened miscarriage while progesterone and Chinese herbs may reduce the risk of miscarriage. However, the quality of these studies is poor. There is no study comparing acupuncture versus control

or other treatments for threatened miscarriage. Further randomized trials with adequate sample sizes are urgently needed in the treatment of threatened miscarriage. The reproductive safety of these treatments should be addressed in further trials as well.

Authors' contribution

Li J and Gao JS contributed equally to this work and are joint first authors.

Conflict of interest

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