Complementary and Alternative Medicine for Threatened Miscarriage: Advantages and Risks

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Threatened miscarriage is one of the most common complications causing pregnancy loss, and it affects approximately 20% of confirmed pregnancies. Even if the miscarriage is avoided, women who suffer from threatened miscarriage remain at high risk for adverse pregnancy outcomes such as premature birth, antepartum hemorrhage, low birth weight, and neonatal death, as well as psychological anomalies [4–8], and thus threatened miscarriage is a physically and psychologically traumatic experience for women and their families. Many factors cause threatened miscarriage, including chromosomal defects, immunological dysfunction, maternal thrombophilic disorders, endocrine abnormalities, and uterine structural anomalies. Additionally, maternal age, previous miscarriage, environmental pollutants, infectious agents, and previous clinical interventions also contribute to a high risk of miscarriage [9–12], and the thorough evaluation of the intrauterine condition with sonography and maternal serum markers might help to diagnose threatened miscarriage or predict subsequent pregnancy outcomes [13]. Bed rest does not significantly reduce the risk of miscarriage, and progesterone and human chorionic gonadotropin (hCG) are most commonly prescribed in women with threatened miscarriage even though little evidence supports their effectiveness [11–13]. Rh prophylaxes like heparin plus aspirin and other regimens such as buphenine hydrochloride have been suggested to be beneficial for threatened miscarriage, but they are associated with adverse events and their effects have not been verified (Figure 1).

The use of complementary and alternative medicine (CAM) for promoting health and treating ailments is an increasing trend worldwide. Studies have reported that women use CAM more than men, and over 80% of women in the UK, 50% of women in Australia, 90% of women in Canada, nearly 25% of women in Denmark, and nearly 50%
Figure 1: Possible etiology and current management of threatened miscarriage.

### What causes it?
- (i) Chromosomal abnormalities
- (ii) Immunological dysfunction
- (iii) Endocrine factors, such as poorly controlled diabetes, polycystic ovary syndrome, and thyroid disease
- (iv) Physical problems with the uterus or cervix
- (v) Infection with bacterial, viral, parasitic, fungal, or sexually transmitted diseases

### What are the risk factors?
- (i) Previous miscarriages ≥2
- (ii) Age >34 years
- (iii) Smoking or drinking
- (iv) Using cocaine or illegal drugs
- (v) History of in vitro fertilization, embryo transfer, or artificial insemination
- (vi) Environmental toxins
- (vii) Low levels of folic acid
- (viii) Certain antibiotics

### How is it managed?
- (i) Bed rest
- (ii) Progesterone
- (iii) Human chorionic gonadotropin
- (iv) Rh prophylaxis
- (v) Other regimens, such as buphenine hydrochloride
- (vi) CAM, including herbal medicines, nutritional supplements, acupuncture, supportive care, or other alternative approaches

2. CHM in Threatened Miscarriage

The prevalence of herbal medicine use by pregnant women ranges between 7% and 79.9% depending on different geographic, social, cultural, and ethnic factors [21, 22, 25, 26]. CHM has a history of about 5000 years, and it has become one of the main therapies in East Asia and has spread to western countries. CHM is widely accepted as an alternative form of medicine, and it is considered beneficial for preventing and treating miscarriage with fewer adverse events compared to current conventional western medicine [10, 27, 28]. There have been a number of cases of treating threatened miscarriage using CHM according to the theory of traditional Chinese medicine (TCM). However, the safety and side effects of using certain herbal medicines during pregnancy is still a matter of debate, and here we review the efficiency and safety of CHM in the treatment of threatened miscarriage.

#### 2.1. Efficiency of CHM for Threatened Miscarriage

Most of the literature regarding CHM use during pregnancy has focused on miscarriage, and the majority of the publications are in Chinese [10, 28, 29]. It has been suggested that the effectiveness of CHM ranges from 79.22% to 100% in the treatment of threatened miscarriage according to randomized and semirandomized trials comparing CHM, conventional western medicine, and combinations of the two (Table 1). However, there is a lack of well-designed placebo-controlled randomized clinical trials. A meta-analysis of 44 randomized clinical trials indicated that CHM alone has a similar efficacy to that of conventional western medicines alone in the treatment of threatened miscarriage, and CHM in combination with other pharmaceuticals was found to be superior to pharmaceuticals alone in maintaining pregnancy after 28 gestational weeks in women with threatened miscarriage [28]. CHM alone or combined with conventional western medicines has also been shown to be more beneficial in improving vaginal bleeding, lower back pain, and abdominal pain [30]. Moreover, a majority of randomized clinical trials and some systematic reviews have demonstrated that a combination of CHM and other pharmaceuticals or psychotherapy might maintain pregnancy and increase the live birth rate for women with recurrent miscarriage [29, 31]. These studies all suggest that CHM has the potential to prevent threatened miscarriage in subsequent pregnancies, but most studies have neglected to investigate the duration, follow-up, adverse events, or toxicity of CHM, and the sample sizes of the interventions have been small.

#### 2.2. Common Formulas and Single CHM for Threatened Miscarriage

A CHM formula contains one or more compositions of herbal raw material and can be available in different preparations such as decoctions, pills, powders, and extracts in order to obtain optimized efficiency. At present, the most commonly used classic prescription for threatened miscarriage is Shoutai Pill [10], which was first described in the book Integrating Chinese and Western Medicine from the late Qing dynasty around 200 years ago. The Shoutai Pill is composed of four ingredients, with Herba Taxilli, Semen Cuscutae, and Radix Dipsaci replenishing the liver and kidney and strengthening the bones and muscles to maintain...
| Formula                      | Main compositions and intervention                                                                 | Comparison                                                                                   | Effective rate | Adverse outcomes*                                                                                                           | References |
|------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|----------------------------------------------------------------------------------------------------------------------------|------------|
| Shoutai pill                 | *Semen Cuscutae* (10–15 g), *Herba Taxilli* (10–20 g), *Radix Dipsaci* (10 g), *Colla Corii Asini* (10 g) PO, QD/BID, 7–28 days, alone or combined with comparators | (A) Progesterone, 20 mg, IM, QD, 7–21 days; (B) progesterone, 40 mg, PO, every other day, to 10 completed weeks of gestation; followed by once every three days to weekly until 12 completed weeks of gestation | 90.00–93.34% | Premature rupture of fetal membranes, gestational diabetes mellitus, gestational hypertension, postpartum hemorrhage, low birth weight infant, neonatal malformation | [34–37]    |
| Zishen Yutai pill           | *Radix Codonopsis*, *Radix Dipsaci*, *Rhizoma Atractylodis Macrocephalae*, *Radix Moriindae Officinalis*, *Fallopia multiflora*, *Cortex Eucommiae* make a pill at 5g PO, TID, 7–21 days, alone or combined with comparators | (A) Progesterone, 20–40 mg, IM, QD, 14–21 days; (B) progesterone, 40 mg, PO, at the first time, followed by 10 mg, Q8H/Q12H, until symptoms disappear; (C) dydrogesterone, 10 mg, PO, BID, 7 days; (D) allylestrenol, 10 mg, PO, QD, 7 days | 85.33–100%    | Colporrhagia, soreness of waist, abdominal pain, hypogastralgia, nausea, dry mouth, poor appetite, constipation, dizziness, headache, and edema | [38–44]    |
| Gushen Antai pill           | *Semen Cuscutae*, *Herba Taxilli*, *Radix Dipsaci*, *Fallopia multiflora*, *Rehmannia glutinosa*, *Cistanche*, *Unciaaria rhyzochyphilla*, *Radix Paoniae Alba*, *Rhizoma Atractylodis Macrocephalae*, *Radix Scutellariae* make a pill at 6g PO, TID, 14–28 days, combined with comparators | (A) Progesterone, 20–40 mg, IM, QD, or 100 mg, PO, BID, 14 days; (B) progesterone, 100 mg, PO, BID, 14 days; (C) dydrogesterone, 40 mg, PO, at the first time, followed by 10 mg, PO, Q8H, 14 days | 87.64–93.90% | Preterm delivery and miscarriage                                                                                          | [45–48]    |
| Andian Ertian decoction     | *Radix Dipsaci* (15 g), *Semen Cuscutae* (15 g), *Herba Taxilli* (15 g), *Pseudostellaria heterophylla* (15 g), *Radix Rehmanniae Praeparata* (10–15 g), *Rhizoma Atractylodis Macrocephalae* (15–20 g), * Dioscoreae Rhizoma* (15 g), *Fructus Corni* (10–15 g), *Dolichos Lablab* (15 g), *Cortex Eucommiae* (9–10 g), *Fructus Lycii* (6 g),*Radix et Rhizoma Glycyrrhizae* (3–6 g) PO, QD/QOD, 7–14 days | Progesterone, 20 mg, IM, QD, 7–90 days                                                                 | 93.33–97.14% | Preterm delivery, miscarriage within 28 weeks                                                                             | [49, 50]   |
| Baoyin decoction            | *Rehmannia glutinosa* (12 g) (6–15 g), *Rehmanniae Radix Praeparata* (6–15 g), *Radix Scutellariae* (4.5–10 g), *Phellodendron chinense Schneid* (4.5–10 g), *Dipodex Rhizoma Alba* (6–10 g), *Radix Dipsaci* (4.5–10 g), *Dioscorea opposita* (4.5–15 g), *Radix et Rhizoma Glycyrrhizae* (3–5 g) PO, BID/TID, 7–21 days, combined with progesterone 100–150 mg PO, BID, 7 days, or dydrogesterone as comparator | (A) Dydrogesterone, 20 mg, PO, Q12H, 21 days; (B) hCG, 2000 IU, IM, QD, 7 days | 90.00–97.40% | Not reported                                                                                                               | [51, 52]   |
Table 1: Continued.

| Formula                  | Main compositions and intervention                                                                 | Comparison                          | Effective rate | Adverse outcomes*       | References  |
|--------------------------|----------------------------------------------------------------------------------------------------|-------------------------------------|----------------|-------------------------|-------------|
| Baotai decoction         | Rehmannia glutinosa (6–15 g) (12 g), Semen Cuscutae (12 g), Herba Taxilli (12 g), Radix Scutellariae (9 g), Poria cocos (9 g), Radix Dipsaci (9 g), Dioscoreae Rhizoma (10 g), Rhizoma Atractyloidis Macrophalae (15 g), Cinnamomum cassia Presl (6 g), Radix Aconiti Lateralis Preparata (3 g) PO, QD, 14 days Semen Cuscutae (10–30 g), Cortex Eucommiae (10–15 g), Herba Taxilli (10–18 g), Radix Dipsaci (10–15 g), Pseudostellaria heterophylla (10–15 g), Radix Astragali (10–15 g), Rhizoma Atractyloidis Macrocephalae (10–15 g), Radix Scutellariae (15 g), Radix Paeoniae Alba (10 g), Rehmanniae Radix Praeparata (10 g), Boehmeriae Radix (10 g), Colla Corii Asini (11 g) PO, BID, 10 days, combined with comparator | Hydrogestrone, 40 mg, PO, once; followed by 10 mg, PO, Q8H, 14 days | 95.00%         | Not reported            | [53]        |
| Bushen Antai decoction   | Semen Cuscutae (10–30 g), Cortex Eucommiae (10–15 g), Herba Taxilli (10–18 g), Radix Dipsaci (10–15 g), Pseudostellaria heterophylla (10–15 g), Radix Astragali (10–15 g), Rhizoma Atractyloidis Macrocephalae (10–15 g), Radix Scutellariae (15 g), Radix Paeoniae Alba (10 g), Rehmanniae Radix Praeparata (10 g), Boehmeriae Radix (10 g), Colla Corii Asini (11 g) PO, BID, 10 days, combined with comparator | Progesterone, 20 mg, IM, QD, 10 days | 79.22–96.00% | Constipation, mouth sores, and asitia | [54, 55]    |

CHM: Chinese herbal medicine; TCM: traditional Chinese medicine; PO: per os; IM: intramuscular; QD: quaque die; Q8H: quaque 8 hours; Q12H: quaque 12 hours; BID: bis in die; TID: ter in die; hCG: human chorionic gonadotropin. *Adverse events occurred when using CHM alone or combined with conventional medicine.
pregnancy and Colla Corii Asini nourishing the yin and blood and further strengthening Qi [32]. The four ingredients are documented in the Chinese Pharmacopoeia and have been approved by the World Health Organization (WHO) for use in clinical trials. The prescription used alone or in combination with western medicines has been shown to be superior to western medicine alone for preventing miscarriage in the first trimester of pregnancy, and no adverse events have been reported [33–37] (Table 1).

On the basis of the Shoutai Pill, professional practitioners have further developed the recipe according to individualized clinical presentations for threatened miscarriage, for example, the Bushen Antai decoction. In addition, the generally applied prescriptions for threatened miscarriage include Baotai decoction, Zishen Yutai Pill, and other recipes that have been shown to be effective. With regard to the theory of TCM, these regimes are considered to regulate Qi and the blood and to improve kidney and spleen function in order to maintain pregnancy. We summarize the studies on the application of common CHM formulas for threatened miscarriage in Table 1 [38–55].

According to TCM theory, threatened miscarriage is due to insufficiency of the spleen and kidney, deficiency of Qi and blood, or both stasis and heat based on syndrome differentiation. Thus, herbal medicines that are frequently used to prevent miscarriage include those that tonify the kidney (e.g., Semen Cuscutae, Herba Taxilli, and Radix Dipsaci), those that tonify Qi and the blood (e.g., Colla Corii Asini and Codonopsis pilosula), those that nourish Qi to invigorate the spleen (e.g., Radix Astragali and Rhizoma Atractylodis Macrocephalae), and those that clear heat and cool the blood (e.g., Radix Scutellariae). Importantly, the proper concerted application of individual CHMs can have synergistic effects. The most commonly used combination is Semen Cuscutae and Herba Taxilli, which are contained in most of the formulas described above and can strengthen the kidney to prevent miscarriage. The most commonly used single compositions of CHM in formulas used to treat threatened miscarriage and prevent further pregnant complications are listed in Table 2 [10, 17, 56–77].

2.3. Potential Mechanism of CHM for Threatened Miscarriage. To explore the molecular mechanism of CHM in threatened miscarriage, many studies have been performed in humans and in diverse animal models both in vivo and in vitro. First, CHM might improve uterine function to retain pregnancy, and it has been reported that Shoutai Pill may reduce the miscarriage rate, increase serum progesterone and estrogen levels [33, 78], enhance endometrial thickness, and regulate the hemodynamic parameters of the uterine spiral artery in order to improve endometrial receptivity and promote implantation [79]. Second, CHM potentially contributes to the development of trophoblasts and reduces the miscarriage rate. For example, Shoutai Pill can regulate the bioactivity behavior of trophoblasts to prevent spontaneous miscarriage by regulating trophoblast proliferation, invasion, and migration capacity, β-hCG secretion by trophoblasts, and apoptosis of trophoblasts in vitro [31, 80]. Furthermore, CHM has the effect of regulating immunological function and anti-inflammatory and antioxidation activities, which is consistent with TCM theory on tonifying the kidney and preventing miscarriage [79, 81, 82]. Shoutai Pill can improve pregnancy outcomes by reducing placental damage and regulating oxidative stress, and Shoutai Pill increases serum IL-2 and IL-6 levels and placental glutathione and superoxide dismutase (SOD) levels and decreases 3,4-methylenedioxymethamphetamine and reactive oxygen species (ROS) levels [82]. Another study found that CHM can treat threatened miscarriage by regulating the expression of the inflammatory factors IFN-γ and IL-10 [83]. Overall, the application of CHM may improve endometrial function, inhibit uterine contraction, regulate immune response, and promote the development of the embryo. However, there are limited numbers of studies into the mechanisms through which individual CHMs or combinations have an effect on threatened miscarriage, and few of the reports are in English.

2.4. Safety and Adverse Events of CHM for Threatened Miscarriage. Almost half of pregnant women in the world use CHMs or other herbal medicines to support their pregnancy, to ameliorate disturbing symptoms and complications, and to reduce the need for western medication, and they widely consider that these treatments are safe and effective. However, all regimes, including CHM, have the potential risk for pregnancy and fetal development, but only a few studies have evaluated the safety of these interventions. CHMs are commonly used in threatened miscarriage in order to prevent pregnancy loss and further complications, and most clinical trials have reported no adverse events or significant risks. Some systematic reviews have concluded, however, that no data are available to demonstrate the safety of CHM for the mother or the infant [29, 31]. In turn, a few studies have found adverse outcomes in relation to CHM, including gastrointestinal reactions, preterm birth, premature rupture of membranes, stillbirth, asphyxia, and infections that cause neonatal death [27]. None of these clinical studies further explained the reasons for these adverse events, and there are limited data available for identifying the risks of CHM. A systematic review and meta-analysis indicated that CHM combined with conventional medicines had lower intervention failures for women with threatened miscarriage, and no obvious differences were found between the combination of CHM and conventional medicine and CHM alone regarding adverse events and toxicity in terms of pregnancy and perinatal outcomes [27]. In the pooled randomized controlled trials, 3.1–22.3% had intervention failure; 2–10% had dry mouth, constipation, and insomnia; 3% had diabetic complications; 5% had preterm delivery; and 1.8% had neurodevelopmental morbidity. Notably, some individual herbal medicines were reported to have potential risks during pregnancy; for example, a Danish prospective cohort study suggested that licorice causes an increase in blood pressure in pregnant women [17] (Table 2).

Moreover, various animal studies have indicated reproductive toxicity with the frequently used CHMs for threatened miscarriage, including fetal resorption, growth
| English name                  | Latin name               | Efficacy based on TCM theory                                                                 | Mechanism of action                                                                 | Adverse events                                                                                     | References       |
|------------------------------|--------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------------|
| Baikal skullcap root         | Radix Scutellariae       | Clearing heat and stopping bleeding to prevent miscarriage                                  | It can have an antiabortive effect through inhibition of maternal-fetal interface immunity, and it contains baikalein, which has anti-inflammatory effects and elevates progesterone levels to prevent miscarriage. | Treatment with 32 g/kg/day led to potential maternal toxicity and major limb abnormalities in mice. | [56–59, 75]     |
| Chinese Angelica             | Radix Angelicae Sinensis | Replenishing and promoting blood circulation, regulating menstruation, relieving pain, and acting as a laxative | The water-based extracts can restrain the mobility of uterine smooth muscle and rectify the excitation of oxytocin. | Inhibited embryonic growth and development in rats and mice.                                     | [60, 75]         |
| Chinese Dodder seed          | Semen Cuscutae           | Tonifying the kidney to prevent miscarriage, benefiting essence, and nourishing yin          | It promotes progesterone secretion, improves trophoblast function, regulates decidual proliferation and apoptosis, and acts as an antioxidant. |                                                                                                   | [61–63, 75]     |
| Chinese Taxillustwig twig    | Herba Taxilli            | Nourishing the liver and kidney, strengthening the waist and knees to prevent miscarriage, dispelling wind, and removing dampness | It is rich in elements such as zinc and manganese that promote fetal development, inhibits uterine contraction, and reduces platelet aggregation. |                                                                                                   | [64, 65, 75]     |
| Donkey-hide glue             | Colla Corii Asini        | Nourishing and regulating the blood to prevent miscarriage, and relieving pain               | It contains iron, zinc, and other essential trace elements and thus can also stop vaginal bleeding, increase circulating calcium levels, and contribute to embryonic development. | Not reported.                                                                                     | [66]             |
| Eucommia bark                | Cortex Eucommiae         | Replenishing the liver and kidney and strengthening bones and muscles to prevent miscarriage | It can weaken pituitrin secretion and suppress uterine contraction.                   | It impacted embryonic growth and development.                                                   | [67, 68, 75]     |
| Himalayan Teasel root        | Radix Dipsaci            | Nourishing the liver and kidney, regulating blood vessels, and strengthening bones and muscles | It suppresses uterine contraction during pregnancy, improves ovarian function, and promotes uterine and embryonic development. | Aqueous extracts at the dosage of 8 or 32 g/kg/d might cause adverse impacts on maternal health and embryonic/fetal development, including maternal death before delivery. | [69, 70, 75]     |
| Largehead Atractylodes rhizome| Rhizoma Atractylodis Macrocephalae | Tonifying Qi and strengthening the spleen                                                   | It contains volatile oils that can promote fetal development and maturity, inhibit uterine contraction, and maintain pregnancy. | Potential reproductive toxicity in pregnant animals within the clinical dose equivalent to that used by humans, such as postpartum maternal mortality, embryonic developmental delay, and major fetal limb abnormalities. | [56, 71, 75, 76] |
| English name              | Latin name                | Efficacy based on TCM theory                                      | Mechanism of action                                                                                                                                                                                                 | Adverse events                                                                                       | References         |
|--------------------------|---------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------|
| Licorice root            | *Radix et Rhizoma*        | Tonifying and regulating Qi and the blood and relieving urgency and pain | It is anti-inflammatory and antioxidative and enhances endogenous steroids. It is also used to relieve abdominal pain and muscle spasms.                                                                         | It can increase blood pressure in pregnant women, and it contains glycyrrhizin (≥500 mg/week) that may result in lower gestational age, increased postpartum maternal mortality, reduced maternal weight gain, and increased early fetal resorption rate in mice. | [10, 17, 75, 77] |
| Milkvetch root           | *Radix Astragali*         | Tonifying Qi and yin, promoting body fluid production, and lifting depression | It elevates placental blood supply and restrains the placental immune response in order to prevent pregnancy complications, and it has benefits for embryonic development.                                         | Not reported.                                                                                       | [72]              |
| Szechwon Tangshen root/  | *Radix Codonopsis*        | Enriching blood and promoting fluid production, strengthening the spleen and benefiting the lung | Its polysaccharide component can strengthen immunity and promote compensatory hematopoiesis of the spleen.                                                                                                  | Antepartum maternal mortality increased in mice.                                                   | [73, 75]          |
| Pilose Asiabell root     |                           |                                                                  |                                                                                                                                                                                                              |                                                                                                       |                   |
| White Peony root         | *Radix Paeoniae Alba*     | Enriching blood, astringing yin, and relieving pain               | It might downregulate fetal Th1/Th2/Th17 cytokines and receptors, which might benefit embryonic survival and development.                                                                                  | Antepartum maternal mortality and perinatal mortality increased in mice.                            | [74, 75]          |

CHM: Chinese herbal medicine; TCM: traditional Chinese medicine.
acupuncture might promote specific beneficial effects in early pregnancy [90, 91]. Acupuncture might thus be a potential alternative option for threatened miscarriage under proper treatment control [11].

The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture for threatened miscarriage [92]. Many experts have raised concerns about the safety of acupuncture for treating women in early pregnancy [93, 94], and there remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy, like SP6, LI4, BL60, BL67, GB21, and LU7. Nevertheless, electro-acupuncture at these forbidden points did not aggravate the miscarriage rate or fetal loss over the course of gestation in pregnant rats [95]. Furthermore, there is no reliable evidence to suggest that acupuncture can induce miscarriage or premature delivery, and the adverse events with the use of forbidden points during pregnancy were similar to the control interventions [95]. The incidence of adverse events probably related to acupuncture during pregnancy was 1.3% according to a systematic review, and most of these were mild adverse events such as needing pain. Severe adverse events and fetal complications due to preterm delivery were rare, and the miscarriage rate was 5%, which was lower than that for control interventions [96]. A recent retrospective cohort study in South Korea reported consistent observations as previous studies, and there were no significant differences in delivery outcomes between pregnancies in the acupuncture and control groups [97]. Even though many of these studies have had small sample sizes and the methodologies have had a high risk of bias, they consistently suggest the safety of acupuncture during pregnancy.

Nowadays, about 4%–13% of pregnant women in Europe receive acupuncture for pregnancy and childbirth issues, and most treatments are given in the first trimester [98, 99]. Acupuncture has been shown to reduce the risk of miscarriage by increasing blood flow to the uterine lining and by aiding implantation, and thus it has potential for the treatment of threatened miscarriage. Professional practitioners are more and more using acupuncture during pregnancy, and surveys on acupuncture use conducted in the UK, Australia, and New Zealand showed that over a half of the acupuncturists had treated women for threatened miscarriages [91]. In a randomized feasibility trial with semistructured participant interviews with 40 women with threatened miscarriage, the participants received a pragmatic acupuncture and moxa protocol or touch intervention with medical self-care advice. The women who received acupuncture on the basis of TCM theory reported reduced vaginal bleeding, cramping, and back pain. These findings demonstrated that acupuncture was a feasible and pragmatic intervention that may be effective for women experiencing threatened miscarriage [92] (Table 3). However, although the application of a pragmatic acupuncture treatment protocol allowed flexibility for diagnosis and treatment, reflecting a treatment approach applicable to the real world, the protocol is difficult to use because the protocol designs do not provide information regarding the specific acupuncture points or needling effects. In addition, it was

### 3. Acupuncture and Moxibustion in Threatened Miscarriage

#### 3.1. The Role of Acupuncture in the Treatment of Threatened Miscarriage

Acupuncture and moxibustion are recognized nonpharmacological and alternative approaches, and they are increasingly used for reproductive conditions worldwide [88, 89]. Based on the theory of TCM, together these treatments have the function of dredging the meridian and stimulating the energy response of the Qi and blood, thereby strengthening the body’s resistance to disease and eliminating pathogenic factors. Traditional acupuncture has specific theories relating to promoting optimal early pregnancy responses, and it is recommended as a treatment modality for threatened miscarriage in acupuncture texts. Although the therapies exist in textbooks, there is yet no quality research to support the use of acupuncture for threatened miscarriage. Within fertility research, acupuncture has been shown to improve hormonal responses with decreased miscarriage rates, thus raising the possibility that acupuncture might promote specific beneficial effects in...
| Approaches               | Acupoints | Intervention                                                                 | Comparison                                                                 | Study design                  | Efficacy rate       | Outcomes                                      | Adverse events | References |
|-------------------------|-----------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------|---------------------|------------------------------------------------|----------------|------------|
| Pragmatic acupuncture   | LU7, LI11, HT7, LR2, LR3, GB30, GB34, GB41, SP1, SP4, ST36, ST37, K16, K19, K21, KI27, BL20, BL23, BL57, BL62, PC6, TE4, TE5, TE6, CV4, GV4, GV20, EX-HN 3 | Needles, moxibustion, and self-care advice. Weekly visits until 12 completed weeks of gestation | A mixed methods study involving a RCT and semistructured interviews | Pregnancy loss: 16.7% vs. 23.8%; pregnancy complication: 11.1% vs. 14.2% | It causes reduced bleeding, cramping, and back pain. | Not reported | [92]        |
| Acupoint sticking       | CV 8      | Dingtai decoction (*Panax ginseng* 30 g, *Radix Angelicae Sinensis* 10 g, *Radix Paeoniae Alba* 15 g, *Cortex Eucommiae* 15 g, *Rehmannia glutinosa Libosch* 15 g, *Rhizoma Atractylodis Macrocephalae* 10 g, *Pericarpium Citri Reticulatae* 5 g, *Radix Glycyrrhizae Preparata* 20 g, *Radix Scutellariae* 15 g, *Semen Cuscutae* 15 g, *Herba Taxilli* 15 g, *Radix Dipsaci* 15 g, *Artemisia Argyi* 15 g, *Amomum Villosum* 3 g), PO, BID, with the herbal residue placed on CV 8 for 6 h for 5 days until vaginal bleeding stops; combined with comparators | hCG, 3000 IU, IM, QD, 3 days; after vaginal bleeding stops, reduce to 3000 IU, IM, QOD; vitamin E, 50 mg, PO, BID; Folic acid, 0.4 mg, PO, QD | RCT 93.3% | The combination is beneficial for improving the symptoms of threatened miscarriage. | Not reported | [103]      |
| Acupoint sticking       | CV 8      | CHM (*Colla Corii Asini* 1 g, *Folium Artemisiae Argyi* 1 g, *Cortex Eucommiae* 1 g, *Fructus Psoraleae* 1 g) placed at CV 8 for 4–6 h per day | Progesterone, 20 mg, IM, QD, hCG, 2000 IU, IM, QD, 14–28 days | RCT 94.83% | Acupoint sticking has a significant effect on early threatened miscarriage. | Not reported | [104]      |
| Approaches                  | Acupoints      | Intervention                                                                 | Comparison                                                                 | Study design | Efficacy rate | Outcomes                                                                 | Adverse events | References |
|----------------------------|----------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------|----------------|--------------------------------------------------------------------------|----------------|------------|
| Acupoint sticking          | CV 8           | CHM (Semen Cuscutae 10g, Radix Dipsaci 10g, Colla Corii Asini 6g, Ramie root 10g, Cortex Eucommiae 10g) placed on CV 8 for 4–6h per day and combined with comparator | Progesterone, 40mg, IM, QD, until symptoms disappear, and change to 20mg, IM, QD, 7 days | RCT          | 90.0%          | The combination can shorten the treatment time, increase serum P level, improve luteal function, prevent subsequent miscarriage, and increase the successful pregnancy rate.   | Not reported   | [105]     |
| Acupoint sticking          | CV 8           | CHM (Cortex Eucommiae 10 g, Ramie root 10 g, Radix Dipsaci 10 g, Semen Cuscutae 10 g, Colla Corii Asini 6 g) placed on CV 8 for 6h per day and combined with comparator | Progesterone, 20mg, IM, QD, 7 days                                           | RCT          | 89.2%          | The combination increased the efficacy rate and improved the clinical symptoms of threatened miscarriage. | Not reported   | [106]     |
| Acupoint sticking          | BL 23, GV4     | CHM (Semen Cuscutae 10 g, Radix Dipsaci 10 g, Colla Corii Asini 6 g, Ramie root 10 g, Cortex Eucommiae 10 g) placed on the acupoints for 4h per day, combined with Bushen Jianpi decoction*, PO, BID, and comparator | Progesterone, 20mg, IM, QD                                                  | RCT          | 93.94%         | The combination can improve threatened miscarriage by inhibiting the secretion of INF-γ, promoting the secretion of IL-10, correcting the pathological shift of Th1/Th2 cytokine balance, and increasing the secretion of hCG and P. | Not reported   | [107]     |
| Auricular acupuncture      | TF5, AT4, CO10, CO15, CO12, AH6a, CO18 | The auricular points were changed every 3 days, for 3 weeks of intervention, and combined with dydrogesterone as comparator | Dydrogesterone, 10mg, PO, BID, until 12 gestational weeks                  | Prospective study | 80.0%          | The combination can promote hematoma absorption and regulate immune factors by reducing Th, Th1/Th2, and serum CA125 level. | Not reported   | [110]     |
| Approaches            | Acupoints                  | Intervention                                                                 | Comparison                                                                 | Study design | Efficacy rate | Outcomes                                                                 | Adverse events | References                  |
|-----------------------|----------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------|----------------|---------------------------------------------------------------------------|----------------|----------------------------|
| Acupoint injection    | ST 36                      | hCG 1000 IU, injected at ST36 and massaged for 3–5 min, alternating on both sides, QOD, 7–10 days, or until a week after symptoms disappear | hCG 1000 IU, IM, QOD, 7–10 days, or until a week after symptoms disappear | RCT          | 91.38–91.7%   | It increased the levels of hCG, E2, and P; decreased the miscarriage rate and treatment time; reduced the amount of conventional medication; and promoted the development of the fetal sac. | Not reported    | [113–115]                   |
| Acupoint catgut embedding | BL 17, BL 18, BL 23, BL 20, BL 21, SP 10, SP 8, KI 7 | Embedding once every two weeks, 6 times, combined with comparator            | Progesterone, 40 mg, IM, QD                                                | RCT          | Successful pregnancy rate: 96.0%; spontaneous abortion rate: 16.7% | Embedding reduced the spontaneous abortion rate, improved the successful pregnancy rate, and regulated hormone levels in patients after IVF-ET. | Miscarriage, and premature birth | [117]                      |
| Moxibustion           | ST 36, PC 6, GV4            | Moxibustion was performed at a distance of 3-4 cm from the patient’s acupoints to make the patient feel moderate heat, 20–30 min, QD. Combined with dydrogesterone, PO, first dose is 40 mg followed by 10 mg, Q8H, until the symptoms disappear | Progesterone, 40 mg, IM, QD, 14 days                                       | RCT          | Successful pregnancy rate: 87.5%                                        | The combinations can increase hCG and P, improve symptoms, and increase the successful pregnancy rate. | Not reported    | [118, 119]                   |

RCT: randomized control trial; CHM: Chinese herbal medicine; hCG: human chorionic gonadotropin; E2: estradiol; P: progesterone; QOD: quaque omni die; Q8H: quaque 8 horas; QD: quaque die; BID: bis in die; PO: per os; IM: intramuscular; IVF-ET: in vitro fertilization-embryo transfer. *Bushen Jianpi decoction composition: Radix Codonopsis 18 g, Radix Astragali Preparata 18 g, Herba Taxilli 15 g, Semen Cuscutae 15 g, Cortex Eucommiae 15 g, Radix Dipsaci 15 g, Radix Paeoniae Alba 15 g, Rhizoma Atractylodis Macrocephalae 12 g, Radix Scutellariae 12 g, Cyperus rotundus 12 g, Radix Glycyrrhizae Preparata 6 g.
reported that different styles of acupuncture treatment had benefits for threatened miscarriage, such as auricular point acupuncture, acupoint sticking, acupoint injection, and catgut embedding [11, 100]. Acupuncture might be a safe therapeutic approach for threatened miscarriage, but the current studies are of poor quality and are usually written in Chinese, and thus further research is required to explore whether acupuncture can reduce the incidence of miscarriage.

3.2. Different Styles of Acupuncture in the Treatment of Threatened Miscarriage

3.2.1. Acupoint Sticking. Acupoint sticking is a noninvasive therapy based on TCM theory in which pastes of various medicinal extract mixtures are placed on the skin at specific acupoints or at the diseased sites. This achieves effects not only through the activities of the drugs, but also by activating acupoints and meridians. Acupoint sticking is generally applied in common chronic diseases, particularly for pain relief [101]. The approach is acceptable for patients and is flexible and safe, and thus a large number of clinical practitioners use the intervention to treat women with threatened miscarriage in China. A meta-analysis investigated the efficacy and safety of different styles of acupuncture in threatened miscarriage and demonstrated that acupoint sticking therapy is the best acupuncture approach for this common pregnancy complication [102]. Generally, acupoint sticking with pastes made from modified CHM formulas combined with oral administration of Chinese herbal decoctions and/or progesterone can reduce the miscarriage rate, and the effectiveness of such combinations has been shown to be better than conventional medicine alone [103–107] (Table 3). However, the efficacy and safety of these treatments are in urgent need of confirmation in future studies.

3.2.2. Auricular Acupuncture. Auricular acupuncture is a therapy based on the stimulation of specific points on the ear. Auricular acupuncture therapy is applied for situations of pain, inflammatory diseases, functional disorders, and endocrine and metabolic disorders by regulating reticular formation and by regulating the sympathetic and parasympathetic nervous systems [108]. This intervention appears to have analogous effects on sedation as opioids and can reduce pain and anxiety [109]. Auricular acupuncture is usually applied as an adjuvant with conventional approaches for relieving pregnancy-related pain and complications. The acupoints on the ear might regulate pregnancy and nourish fetal developing by achieving chronic shallow acupressure. TCM practitioners reported that a combination of auricular acupuncture and dydrogesterone could promote hematoma absorption in women with threatened miscarriage in early pregnancy complicated with subchorionic hematoma, was more effective than dydrogesterone alone, and could regulate immune factors over a 3-week course of treatment [110] (Table 3).

3.2.3. Acupoint Injection. Acupoint injection, which is also called pharmacoacupuncture, aqua acupuncture, water acupuncture, or herbal acupuncture, is widely used in East Asia and is based on the same meridian theory of acupuncture. Acupoint injection therapy is the combination of acupuncture and medications and has been demonstrated to benefit patients with nonspecific chronic low back pain [111]. The injection of sterile solutions of Chinese herbal extracts or western medicines into acupoint locations leads to synergistic therapeutic effects of acupuncture, medicine, and meridian activation. The drugs are absorbed through the subcutaneous tissues and capillary vessels, while the needles give positive stimulation at local acupoints, which may promote local blood circulation, elevate metabolic ability, and ameliorate the pathology while promoting inflammation resolution [112]. Many studies have found that acupoint injection therapy has a significant effect on threatened miscarriage compared to western medicine alone in reducing early pregnancy loss. The most common therapy is injection of 1000 IU of hCG into the Zusanli acupoint (ST 36) every other day [102, 113–115] (Table 3). This method is safe and reliable, with little side effects, and it treats diseases through the combined action of drugs and acupoints. More well-designed studies are needed to determine the efficacy and safety of acupoint injection therapy for threatened miscarriage.

3.2.4. Acupoint Catgut Embedding. Acupoint catgut embedding refers to embedding absorbable catgut sutures into certain acupoints, and the continuous stimulation of acupoints is believed to cure diseases and strengthen the body. Catgut embedding at acupoints evolved from needle embedding at acupoints by replacing needles with catgut, and this not only has effects similar to standard acupuncture, but also has effects due to the prolonged stimulation time, which can reach 2 weeks or even longer. The approach showed a tendency for equal effects compared to other kinds of acupuncture for reducing abdominal obesity, but the approach had fewer reported adverse events [116]. Acupoint catgut embedding has also been indicated to prevent miscarriage in patients with threatened miscarriage. In a randomized control trial, the patients who had experienced in vitro fertilization-embryo transfer were treated with catgut embedding once every two weeks until 12 weeks of gestation. The early miscarriage rate was 16.7%, and the pregnancy rate was 96.0%; these were significantly lower and higher, respectively, compared to those who received progesterone [117] (Table 3). It thus seems that acupoint catgut embedding is beneficial for threatened miscarriage and is worth further investigation.

3.2.5. Moxibustion. Moxibustion consists in burning the leaves of Chinese mugwort (Artemisia vulgaris) close to the skin to induce heat at certain acupoints. The intention is to warm up and invigorate the flow of Qi while also eliminating various pathogenic influences on the body. This therapy is considered safe and has no side effects, making it a viable
solution for pregnant women looking for a remedy for pregnancy-related symptoms. Two randomized, controlled studies in China looked at the combination of daily moxibustion and dydrogesterone compared to progesterone intramuscular injection or dydrogesterone oral administration. The moxa was placed over the acupoints Zusanli (ST36), Neiguan (P6), and Mingmen (GV4), and the combination approach was superior to progesterone or dydrogesterone alone in decreasing the miscarriage rate in women with threatened miscarriage [118, 119] (Table 3). In contrast, it has been reported that moxibustion can stimulate estrogen and prostaglandin production and increase fetal activity and uterine contractions in order to reduce non-cephalic presentations at birth [120]. Thus, the safety and efficacy of moxibustion in the treatment of threatened miscarriage are still a matter of debate.

4. Nutritional Supplements in Threatened Miscarriage

Nutritional supplements, also known as dietary supplements, are used as an auxiliary way of supplying amino acids, trace elements, vitamins, and minerals for maintaining maternal health and fetal development. Dietary habits constitute important risk factors for potentially harmful nutritional deficiencies in pregnant women, and inadequate diet and nutritional supplementation during pregnancy can damage placental function and increase the risk of miscarriage and other pregnancy complications [24, 121, 122]. Nutritional supplements include essential nutrients to maintain human health, and vitamins and trace elements can directly affect the growth and development of the fetus. Mineral elements and vitamins can maintain the activity of the internal environment and various biochemical substances, and they participate in the body’s energy transfer and metabolic regulation. Therefore, it is of great significance to give nutritional supplements before and during pregnancy because adequate nutritional support for pregnant women is essential for maintaining their own health and for supporting fetal development, growth, and future outcomes.

Oxidative stress can also lead to increased risk of threatened miscarriage, spontaneous abortion, recurrent pregnancy loss, and preeclampsia [123, 124]. Antioxidant supplementation may be effective in controlling the production of ROS and combating damage caused by free radicals, and it continues to be explored as a potential strategy for overcoming pregnancy disorders associated with miscarriage [124]. Natural antioxidant compounds alone or in combination with other antioxidants or micronutrients during pregnancy may have the potential to prevent pregnancy loss and other complications [123]. Nutritional supplements and antioxidant intake are usually within the dietary reference intake range, which includes the effects of food and fortified foods, and only a few minor adverse events, such as gastrointestinal reactions, have been shown to occur [125]. Here, we review studies on the efficacy and safety of nutritional supplements for women with threatened miscarriages.

4.1. Essential Trace Elements. Essential trace elements are involved in various biochemical pathways, and they play a crucial role in maternal health and fetal growth and development during pregnancy [126, 127]. Alterations in the concentrations or homeostasis of these micronutrients during pregnancy appear to be closely linked to various disorders and adverse pregnancy outcomes like miscarriage, preterm delivery, stillbirth, intrauterine growth restriction, fetal malformations, and premature rupture of membranes. Trace elements have been shown to facilitate various vital biochemical reactions by acting as cofactors for many enzymes and by stabilizing the structures of enzymes and proteins, and they are significant for all levels of cellular functions [128, 129]. It may be necessary to supplement essential trace elements in women with threatened miscarriage [126, 130].

Zinc (Zn) is one of the most important essential trace elements in humans, and it participates in multiple biological functions including protein synthesis, cellular division, and nucleic acid metabolism [131]. Zn deficiency during pregnancy gives rise to the risk of pregnancy loss, preeclampsia, placental abruption, preterm birth, low birth weight, birth defects, circulatory disorders, immune response impairments, and psychological disorders [132–135]. Women with threatened miscarriage have been shown to have 35.7% lower Zn levels than healthy pregnant women [126, 136], and low serum Zn levels during the early weeks of pregnancy have been shown to lead to miscarriage and fetal congenital malformations by reducing cell proliferation and protein synthesis, which is associated with increased cellular oxidative damage and apoptosis [126, 137]. Also, it was shown that women with serum Zn levels below 10.5 μmol/l had a miscarriage rate of 23.5%, and adding supplements reduced the rate to 2% [138]. However, studies of the effects of Zn supplementation during pregnancy have shown inconsistent results, possibly in part because of the challenges in establishing the baseline Zn status in different populations [139]. Zn supplementation at 30 mg daily did not seem to confer any benefit on infants’ mental development among poor women in Bangladesh [140]. Zn supplementation might be prudent for women with poor gastrointestinal function, but the evidence was limited for beneficial effects of general Zn supplementation during pregnancy, and such treatment should be considered with caution.

Copper (Cu) as a trace element plays an important role in the maturation of hematopoietic cells in normal pregnancy and embryogenesis and in fetal and postnatal growth, and low plasma Cu levels have been found in spontaneous, threatened, and missed miscarriages during the first trimester of pregnancy [141]. Women with threatened miscarriage had 47.0% lower Cu levels than women with healthy pregnancies, and approximately 30% failed to reach term due to Cu deficiency [136, 142, 143]. There is a direct and positive correlation between Zn and Cu levels in women with threatened miscarriage, and there is a significant negative correlation between Cu and the ratio of Cu to Zn in women with a history of spontaneous abortion. Both Zn and Cu have a positive role in pregnancy outcomes, and optimum levels of Zn and Cu might be able to reduce the
occurrence of spontaneous miscarriage [133, 136]. Women who are Cu deficient usually take supplements of 1 mg of Cu daily and 30 mg of Zn separately for 14 days in order to normalize decreased SOD function [140]. In contrast, some studies found maternal serum Cu levels to be increased in threatened miscarriage compared with healthy pregnancy due to the increase of ceruloplasmin as a result of elevated levels of estrogen [126, 144–146]. Thus, there is a debate as to whether women with threatened miscarriage should be treated with Cu supplements.

Iron (Fe) is a component of hemoglobin and myoglobin, and it supports maternal erythropoietic expansion and fetal growth and development during pregnancy. It is also involved in the transport, storage, and use of oxygen [147]. Fe deficiency is associated with increased oxidative stress, placental and fetal hypoxia, and reduced immunity during pregnancy. Previous studies found that serum Fe levels were lower in cases of threatened miscarriage, and the serum Fe level might be an important diagnostic and prognostic parameter [126, 148]. Pregnancy loss is associated with profound changes in maternal Fe metabolism [149], and maternal Fe deficiency, which is common in pregnant women [150], negatively impacts the mother’s health and fetal development and increases the risk of prenatatal and postnatal complications. Foods rich in Fe include red meat, shellfish, eggs, beans, and leafy green vegetables, and high Fe intake with higher Fe bioavailability is needed by pregnant women to prevent adverse pregnancy outcomes and to meet the needs of the fetus. Pregnant women should routinely receive Fe supplements tailored according to serum ferritin levels. The International Nutritional Anemia Consultative Group recommends oral ferrous iron supplementation at 60 mg/day during pregnancy to prevent Fe-deficiency anemia. Depending on the severity of anemia, international guidelines recommend elemental ferrous iron at 100–200 mg daily or 60 mg twice daily as the first-line treatment [151–153]. Prolonged-released ferrous sulfate (ferrous sulfate–polymeric complex) has the lowest incidence of adverse events of all the available supplements, and this has positive implications for compliance [121]. Moreover, the metabolism of essential trace elements is closely related. For example, Fe deficiency results in an increase in liver Cu levels [126], high intakes of supplemental Fe or the presence of any gastrointestinal disease can interfere with Zn absorption, and Zn and selenium supplementation need to be given along with Fe during pregnancy [154]. The available evidence suggests that Fe supplements are needed for pregnant women, but overtreatment should be avoided.

Magnesium (Mg) and manganese (Mn) are additional essential trace elements for metabolic regulation, and serum Mg and Mn levels have been reported to be lower in women with threatened miscarriage compared to those with a healthy pregnancy [126]. Mg deficiency is associated with hypertension, preeclampsia, placental dysfunction, and premature labor in pregnant women, but Mg levels have not been shown to be different between pathological pregnancies and healthy controls [155]. Furthermore, some studies have reported that Mn concentrations are increased in women with a history of miscarriage [156]. There is still limited evidence for the use of Mg and Mn supplements for the treatment of threatened miscarriage.

4.2. Vitamin Supplements. Vitamins are essential nutrients to maintain metabolism, physical growth, and development and to prevent disease. Nearly 30% of pregnant women suffer from a vitamin deficiency, and about 75% of these would show a deficit of at least one vitamin in the absence of prophylaxis [157]. Vitamin supplementation during pregnancy may prevent adverse pregnancy outcomes and reduce the risk of pregnancy loss [24], but there are still contradicting findings in the research on vitamin supplements and the risk of miscarriage. Insufficient vitamin intake is related to an increased risk of miscarriage, and the intake of multivitamins with Fe and folic acid may decrease the risk of stillbirth, but single vitamin supplements either before or during early pregnancy have not been shown to reduce the miscarriage rate [24, 158, 159].

Vitamin A is a crucial micronutrient for pregnant women and their fetuses, and vitamin A can reduce the risk of anemia, infection, and night blindness in pregnant women [157, 160, 161]. Vitamin A deficiency is prevalent in developing countries, and it impairs Fe status and reduces resistance to infections [157]. In a systematic Cochrane review, there was no positive effect on the total risk of fetal loss, on early or late miscarriage, or on stillbirth in women who received vitamin A with any other combination [24]. Vitamin A supplements enhance infant birth weight and growth in HIV-infected women [157]. The recommended upper limit for vitamin A supplements is 3000 IU/day, but when used in excess during the first trimester of pregnancy, such levels can have teratogenic effects on the first 60 days following conception [160]. However, there is no evidence of vitamin A supplements leading to congenital malformations or other adverse effects [24]. Further research is needed on the dose and duration of vitamin A supplements during pregnancy, especially its use for threatened miscarriage.

Vitamin B complex plays a crucial role in maternal health and fetal development. Vitamin B facilitates the metabolism of homocysteine, and vitamins B6 and B12 determine the homocysteine concentration in the blood, while disturbances in maternal and fetal homocysteine metabolism may result in miscarriage, and hyperhomocysteinemia is considered a risk factor for recurrent miscarriage [162, 163]. Vitamin B6 deficiency is associated with miscarriage, preeclampsia, gestational carbohydrate intolerance, hyperemesis gravidarum, and neurological diseases in infants [157]. Supplementation with vitamin B6 has been shown to reduce the chance of miscarriage by 50% and to prevent stress from affecting fetal growth [164, 165]. Vitamin B6 has also been indicated to improve insulin resistance and to reduce oxidative DNA damage and C-reactive protein, and it may act similarly on progesterone and reduce prolactin in order to prevent miscarriage [166, 167]. Vitamin B12 deficiency is associated with recurrent early pregnancy loss, and the miscarriage risk increases by 3.8-fold with every quartile of severity in vitamin B12 deficiency [168, 169]. Vitamin B12 supplementation has been shown to
lead to successful pregnancy in 80% of women with vitamin B12 deficiency [170]. Deficiency in the conversion of vitamin B3 into nicotinamide adenine dinucleotide causes congenital malformations and miscarriages in mouse models, and vitamin B3 supplementation has been shown to prevent miscarriages and birth defects [171, 172]. However, recent reviews of the literature indicate that there is insufficient evidence for the benefits and harms of routine vitamin B supplementation in humans for threatened miscarriage.

Folate, also known as vitamin B9 and folacin, is one of the B vitamins. Folate deficiency may lead to congenital malformations, anemia, spontaneous abortions, pre-eclampsia, intrauterine growth restriction, and placental abruption. Clinicians commonly recommend that patients start or continue to take prenatal vitamins with folic acid supplementation in order to prevent neural tube defects and preeclampsia. A daily supplemental dose of 400 μg/day of folic acid is recommended when planning pregnancy, starting from 2 months before to 3 months after conception [121]. Women at high risk for folate deficiency should receive supplemental folic acid at 4-5 mg/day [173–177]. Evidence demonstrates that low dietary folate is associated with high risk of miscarriage [178], but the risk of early or late miscarriage is not reduced with folic acid supplementation alone or with other combinations according to a meta-analysis, and there appears to be no difference between women receiving folic acid and those who do not in terms of congenital malformations and stillbirths [24].

Vitamin C is an essential nutrient involved in the repair of tissue and the enzymatic production of certain neurotransmitters, and it is vital for both maternal and fetal health. Foods high in vitamin C include citrus fruits, tomatoes, and broccoli, and a balanced diet that is high in Fe and vitamin C is beneficial for a healthy pregnancy. However, vitamin C levels tend to be low in women who have a miscarriage, and supplementation of vitamin C may reduce the risk of miscarriage [179]. Further, vitamin C supplements increase maternal progesterone levels, improve psychological disorders, and may be of benefit to prevent miscarriage and decrease the development of preeclampsia [180, 181]. Nevertheless, there is insufficient data to support the role of vitamin C supplementation alone or combined with vitamin E in reducing total fetal loss, the risk of early or late miscarriage, the risk of stillbirth, or the risk of congenital malformations or adverse events [24]. Supplementation with vitamin C may be beneficial for threatened miscarriage, but overdosing should be avoided [157].

Vitamin D mainly regulates the amount of calcium and phosphate needed to keep bones, teeth, and muscles functioning properly. Vitamin D requirements are increased during pregnancy in order to adapt to the heightened physiological demands in the mother, including driving the formation of the fetal skeleton and maintaining an environment that is tolerant of paternal and fetal tissues and their associated alloantigens [182, 183]. It is estimated that 20%–60% of pregnant women in the UK, 10%–40% in the USA, and 30%–50% in Australia, India, and Saudi Arabia have a vitamin D deficiency [184–188]. Vitamin D deficiency may increase the risk of threatened miscarriage, and it is also related to adverse outcomes during pregnancy. Several observational studies demonstrated that serum 25-hydroxyvitamin D (25(OH)D) levels in women with threatened miscarriage tend to be lower than those in women with normal pregnancy, suggesting that low serum levels of vitamin D can be considered a risk factor for threatened miscarriage [189–191]. Global reports suggest that 40%–98% of pregnant women have 25(OH)D levels below 50 nmol/L and 15%–84% have levels below 25 nmol/L [192, 193]. Importantly, vitamin D-binding protein (VDBP) levels are often low in maternal serum, and such deficiencies are associated with miscarriage and adverse pregnancy outcomes including preeclampsia, preterm birth, and fetal growth restriction [194]. VDBP is expressed at low levels in the placenta and decidua in spontaneous miscarriages, and it might serve as a potential biomarker for miscarriages and has implications in the pathophysiology of spontaneous miscarriage [195]. Supplementation with vitamin D seems to be beneficial for threatened miscarriage [157], and a randomized double-blinded study showed that supplementation with vitamin D3 (400 IU/day) led to a decreased incidence of miscarriage and serum IL-23 levels in women with unexplained recurrent spontaneous abortion [196]. Vitamin D supplementation can reduce inflammation and is useful as immunotherapy to prevent miscarriage by downregulating IL-2, IFN-gamma, and TNF-alpha gene transcription [197, 198]. The daily upper safe limit for vitamin D has been set at 4000 IU, and the recommended dose of vitamin D is 1000–2000 IU, which can be supplemented daily in the second and third trimesters without fear of toxicity or teratogenicity. However, no safety data are available for this dose during the first trimester [199].

Vitamin E is important for the proper functioning of many organs, and it is an antioxidant that helps to inhibit processes that damage cells. Low vitamin E levels may be linked to greater miscarriage risk [200, 201]. Vitamin E in combination with aspirin is effective in improving uterine artery blood flow in women with recurrent miscarriage and thus prevents pregnancy loss and other complications [158]. A Hungarian case-control study reported that vitamin E supplements at a dose 450 mg daily are frequently used for the prevention of threatened miscarriage and lead to a nearly one-third reduction in preterm births in pregnant women, although internationally this method is no longer recommended [202]. The use of vitamin E, although generally considered “healthy,” may be harmful to the pregnancy outcome by disrupting the physiological oxidative gestational state and is consequently not recommended to prevent preeclampsia [157]. In a placebo-controlled, double-blind trial, women diagnosed with chronic hypertension or who had a prior history of preeclampsia who received daily doses of vitamin E (400 IU) and vitamin C (1000 mg) had an increased risk of premature rupture of membranes [203], while another study did not confirm the teratogenic effects of the relatively high-dose vitamin E intake in pregnant women [204]. Further studies are needed on the effect and safety of vitamin E for threatened miscarriage and during early pregnancy.
Multivitamin supplements are widely used by pregnant women. Multivitamins together with iron and folic acid are commonly recommended to improve birth outcomes and reduce the risk of miscarriage, and Cochrane reviews have shown that a multivitamin plus iron and folic acid can decrease the risk of stillbirth but with no significant effect on the overall risk of fetal loss or miscarriage compared with placebo, folic acid, or vitamin A alone [24, 122]. In all other analyses of the effect of multivitamin supplementation on total fetal loss or early or late miscarriage, there were no differences between groups, including multivitamins versus control, multivitamins with vitamin E versus multivitamins without vitamin E or control, and multivitamins with Fe and folic acid versus Fe and folic acid alone. Only a few trials found that multivitamins with or without vitamin A can reduce total fetal loss; however, these findings should be interpreted with caution due to small sample sizes [24]. In addition, studies have suggested that the use of multivitamin supplements within the range of the dietary reference intakes does not result in excess intake and does not increase mortality, and only minor adverse effects such as gastrointestinal symptoms have been reported with multivitamin supplements [125, 205].

4.3. Other Antioxidants. Oxidative stress has been recognized as one of the main mediators of female infertility by causing various reproductive pathologies such as polycystic ovary syndrome (PCOS), preeclampsia, miscarriage, and unexplained infertility [123]. When oxidative stress develops too early in pregnancy, it can impair placental development and/or enhance syncytiotrophoblastic degeneration, culminating in pregnancy loss [206]. Nowadays, concerned women prefer dietary supplements with antioxidant properties over synthetic drugs as a natural way to lessen the oxidative stress and enhance their fertility and to prevent early pregnancy loss, with the idea of replacing depleted antioxidant stores to combat an overwhelmingly oxidative environment. However, a meta-analysis of relevant studies found no supporting evidence for any beneficial effects of antioxidant supplementation [207]. Thus, caution must be still used in the application of antioxidants during pregnancy. The most commonly used antioxidants for pregnant women are vitamins, alpha-lipoic acid (ALA), and N-acetylcysteine (NAC), and future randomized controlled clinical trials in humans based on current animal or in vitro studies are necessary to elucidate the precise mechanisms through which oxidative stress affects female reproduction.

ALA is a natural antioxidant synthesized by plants and animals [208], and it has been shown to prevent miscarriage by reducing the levels of proinflammatory cytokines, such as TNF-alpha, IL-1 beta, IL-6, IL-8, IL-17, and INF-gamma, and by inducing anti-inflammatory IL-10 release. In addition, ALA can induce vascular endothelial growth factor to stimulate tissue epithelialization, collagen deposition, and smooth muscle actin fibrogenesis in order to resolve subchorionic hematoma in threatened miscarriage [209–212]. ALA is able to reduce ROS levels and increase the total antioxidant capacity in cultured preantral mouse follicles [213]. In randomized controlled trials, ALA supplementation alone at a dose of 10 mg or 600 mg or combined with vaginal progesterone could prevent pregnancy loss; reduce the symptoms of vaginal bleeding, abdominal pain, and uterine contractions; and promote choriocytic hematoma reabsorption in pregnant women with threatened miscarriage compared to pregnant women without intervention or pregnant women treated with progesterone alone [214, 215]. However, there was no statistical difference in the improvement of symptoms of threatened miscarriage, and the sample size was small. In order to further confirm the role of ALA in improving threatened miscarriage in pregnant women and to verify its safety, well-designed clinical studies with larger sample sizes should be conducted [208, 209, 216].

NAC is a commonly used mucolytic drug, and it not only increases cellular antioxidant levels, but also improves insulin receptor activity in human erythrocytes and regulates the secretion of insulin in response to glucose uptake [217]. The supplement can prevent endothelial damage and biological effects caused by oxidants in non-insulin-dependent adult diabetics by preventing ischemia, inhibiting phospholipid metabolism, and promoting inflammatory cytokine release and protease activity [218]. NAC might have potential benefit for threatened miscarriage, and some studies have shown that NAC significantly improves the pregnancy rate and ovulation rate compared with placebo [218, 219]. However, some studies have shown that there is no significant difference in miscarriage rate between NAC supplementation and placebo in PCOS patients [218]. In addition, in a randomized controlled trial of PCOS patients with clomiphene citrate resistance, the live birth rate was higher after treatment with a combination of metformin and clomiphene citrate compared to treatment with NAC [220]. NAC was suggested to reduce fetal loss in a PCOS rat model; however, it was shown that supplementation with NAC could induce miscarriage in control pregnant rats [221]. Considering the poor quality of existing studies and the lack of studies assessing miscarriage rates, well-designed randomized controlled trials for threatened miscarriage are needed.

Omega-3 is a fatty acid that may have potential for preventing miscarriage. In a prospective study, omega-3 combined with aspirin improved the uterine artery blood flow velocity in women with recurrent miscarriage [222]. However, the literature on the relationship between human serum omega-3 concentration and reproduction is limited specifically to infertile people, and whether it can prevent miscarriage is still controversial [223, 224]. Therefore, more research is needed to clarify the role of omega-3 and how it can be used more effectively.

At present, there are few studies focusing on the role of nutritional supplements as treatments for threatened miscarriage. Overall, current studies indicate that deficiencies in several trace elements (Zn, Cu, Fe, Mg, and Mn) and vitamins (A, B, C, D, E, and folate) are associated with high risk of pregnancy loss. In particular, low levels of Zn, Cu, Fe, and vitamin D may result in threatened miscarriage. Thus, proper supplementation with Zn, Cu, Fe, vitamin D, vitamin E, and ALA may have efficacy as treatments for threatened
m miscarriage and in preventing further complications. Although many studies have sought to clarify the positive effects of nutritional supplements such as trace elements, vitamins, and antioxidants on threatened miscarriage, most of them are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. Therefore, it is necessary to carefully design more high-quality studies to clarify the specific effects of nutritional supplements on threatened miscarriage, as well as their safety and tolerance, so as to better provide care for pregnant women. Moreover, there is currently insufficient evidence to determine the effects of different combinations of nutritional supplements on threatened miscarriage.

5. Psychological Interventions and Other CAM Therapies in Threatened Miscarriage

Of all clinically recognized pregnancies, a quarter to a third experience a threatened miscarriage. Miscarriage is often a physically and psychologically traumatic event for these women and their families, and women may suffer psychological morbidities such as stress, anxiety, depression, and grief as a reaction to miscarriage [225]. The psychological distress can last between one and three years after a miscarriage and may affect the woman’s quality of life and subsequent attempts to become pregnant [226]. Additionally, psychological distress can impact the fetus and result in preterm birth or low birth weight, and it can result in long-term consequences for the child such as deficits in cognitive functioning and an increase in negative behavior [227, 228]. Despite the potential of follow-up care or emotional support for negative outcomes, more than half of women do not receive psychological interventions at the time of miscarriage. [229], thus there is a need to find ways to mitigate psychological distress in order to prevent miscarriage.

CAM approaches may help women to regulate their emotions during the current pregnancy or after a miscarriage, and this can be beneficial for the offspring. Psychological interventions may help women to regulate their emotions and promote psychosocial well-being during the current pregnancy or after a miscarriage, and this can be beneficial for the offspring. Most clinical trials have reported no adverse events or significant risks, but systematic reviews have concluded that no data are available to demonstrate the safety of CHM for the mother or the infant with current publications. In addition, animal studies indicate that the frequently used CHMs have reproductive toxicity for threatened miscarriage, including fetal resorption, growth restriction, and congenital malformations. The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture and moxibustion for threatened miscarriage. There remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy.

Most studies are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. There is little evidence to suggest that psychological interventions are beneficial in improving psychological morbidity to prevent threatened miscarriage.

| CAM therapies                  | Efficiency                                                                 | Safety and risk                                                                 |
|--------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| CHM                            | CHM may improve endometrial function, inhibit uterine contraction, regulate immune response, and promote the development of the embryo. It is considered beneficial for preventing and treating miscarriage with fewer adverse events compared to current conventional western medicine by being used alone or in combination with western medicines. Acupuncture, acupoint sticking, auricular acupoint, acupoint injection, acupoint catgut embedding, and moxibustion are recognized as nonpharmacological approaches, which can maintain pregnancy, and enhance the effects with the CHM or western medicines. Most studies show that acupuncture is safe and effective without side effects. Nutritional supplements are used as an auxiliary way of supplying amino acids, trace elements, vitamins, and minerals for maintaining maternal health and fetal development. Proper supplementation with Zn, Cu, Fe, vitamin D, vitamin E, and ALA may have efficacy as treatments for threatened miscarriage and to prevent further complications and is convenient to supplement. Psychological interventions may help women to regulate their emotions and promote psychosocial well-being during the current pregnancy or after a miscarriage, and this can be beneficial for the offspring. | Most clinical trials have reported no adverse events or significant risks, but systematic reviews have concluded that no data are available to demonstrate the safety of CHM for the mother or the infant with current publications. In addition, animal studies indicate that the frequently used CHMs have reproductive toxicity for threatened miscarriage, including fetal resorption, growth restriction, and congenital malformations. The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture and moxibustion for threatened miscarriage. There remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy. Most of studies are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. There is little evidence to suggest that psychological interventions are beneficial in improving psychological morbidity to prevent threatened miscarriage. |
| Acupuncture and moxibustion     | Most clinical trials have reported no adverse events or significant risks, but systematic reviews have concluded that no data are available to demonstrate the safety of CHM for the mother or the infant with current publications. In addition, animal studies indicate that the frequently used CHMs have reproductive toxicity for threatened miscarriage, including fetal resorption, growth restriction, and congenital malformations. The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture and moxibustion for threatened miscarriage. There remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy. Most of studies are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. There is little evidence to suggest that psychological interventions are beneficial in improving psychological morbidity to prevent threatened miscarriage. | Most clinical trials have reported no adverse events or significant risks, but systematic reviews have concluded that no data are available to demonstrate the safety of CHM for the mother or the infant with current publications. In addition, animal studies indicate that the frequently used CHMs have reproductive toxicity for threatened miscarriage, including fetal resorption, growth restriction, and congenital malformations. The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture and moxibustion for threatened miscarriage. There remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy. Most of studies are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. There is little evidence to suggest that psychological interventions are beneficial in improving psychological morbidity to prevent threatened miscarriage. |
| Nutritional supplements         | Nutritional supplements are used as an auxiliary way of supplying amino acids, trace elements, vitamins, and minerals for maintaining maternal health and fetal development. Proper supplementation with Zn, Cu, Fe, vitamin D, vitamin E, and ALA may have efficacy as treatments for threatened miscarriage and to prevent further complications and is convenient to supplement. Psychological interventions may help women to regulate their emotions and promote psychosocial well-being during the current pregnancy or after a miscarriage, and this can be beneficial for the offspring. | Most clinical trials have reported no adverse events or significant risks, but systematic reviews have concluded that no data are available to demonstrate the safety of CHM for the mother or the infant with current publications. In addition, animal studies indicate that the frequently used CHMs have reproductive toxicity for threatened miscarriage, including fetal resorption, growth restriction, and congenital malformations. The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture and moxibustion for threatened miscarriage. There remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy. Most of studies are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. There is little evidence to suggest that psychological interventions are beneficial in improving psychological morbidity to prevent threatened miscarriage. |
| Psychological interventions     | Psychological interventions may help women to regulate their emotions and promote psychosocial well-being during the current pregnancy or after a miscarriage, and this can be beneficial for the offspring. | Most clinical trials have reported no adverse events or significant risks, but systematic reviews have concluded that no data are available to demonstrate the safety of CHM for the mother or the infant with current publications. In addition, animal studies indicate that the frequently used CHMs have reproductive toxicity for threatened miscarriage, including fetal resorption, growth restriction, and congenital malformations. The safety of acupuncture in pregnancy is reasonably well accepted, but there is still a lack of high-quality scientific research to validate the safety and effectiveness of acupuncture and moxibustion for threatened miscarriage. There remains a debate regarding the needling points that are historically considered to be forbidden during pregnancy. Most of studies are of low quality and controversial because of their small sample sizes, poor and inconsistent reporting of methods, excessive confounding factors, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. There is little evidence to suggest that psychological interventions are beneficial in improving psychological morbidity to prevent threatened miscarriage. |

CAM: complementary and alternative medicine; CHM: Chinese herbal medicine; Zn: zinc; Cu: copper; Fe: iron; ALA: alpha-lipoic acid.
turn control mood [233, 234]. Future research in this area is needed to establish the effectiveness of complementary approaches in pregnant women and to provide evidence for strategies that healthcare providers can use when treating their patients.

6. Summary

We have reviewed the primary literature focusing on the research into the application of CAM in women with threatened miscarriage, with an emphasis on the efficacy and safety of the treatments. In general, CHM, acupuncture and moxibustion, nutritional supplements, and psychological interventions are the most commonly used to prevent pregnancy loss or complications, and they have proven beneficial for the treatment of threatened miscarriage. We briefly summarize the efficacy and safety of various CAM approaches in the treatment of threatened miscarriage (Table 4). Commonly, the CAM therapies are combined with luteal support medications such as progesterone and/or hCG for threatened miscarriage. It is suggested that pregnancy loss had a deficiency of progesterone and hCG, and low levels of maternal serum progesterone or hCG in early pregnancy may be adverse prognostic factors for threatened miscarriage [12, 13, 235]. Hence, supplementation with progesterone or hCG may prevent miscarriage and maintain pregnancy; however, the evidence remains conflicting. Although the meta-analysis indicated that progesterone may reduce the rate of spontaneous miscarriage but has little effect in the preterm birth, and hCG may have no significant effect in women with threatened miscarriage, the evidence is insufficient and of poor quality [12, 13, 236]. Currently, luteal support medications are still main management for threatened miscarriage in clinic. Moreover, majority of data show that the combination of CAM and luteal support medications may increase maternal circulation progesterone and hCG levels, which seems to be more beneficial than that medication alone for maintaining pregnancy and promoting psychosocial well-being in women with threatened miscarriage. However, whether the use of CAMs is main or adjuvant therapy is still unsure. Therefore, not only CAM approaches but also luteal support drugs need further research with good-quality evidence to determine the effects in threatened miscarriage.

However, issues of safety and risks with the use of CAM during early pregnancy require further studies. At present, there is little evidence to indicate whether CHM, acupuncture, and supplements are harmful for fetal development or whether they induce pregnancy loss, premature delivery, or stillbirth. It would be beneficial to conduct large-scale, randomized clinical trials in the future to determine the efficacy and safety of CAM, to help substantiate its therapeutic effects, and to identify possible adverse events. As the Chinese idiom goes “take the essence and discard the dregs,” we need further investigations to develop effective and safe CAM therapy regimes during pregnancy to support both the mother and her baby.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions

Min Hu contributed to the original draft and takes responsibility for the integrity of the final manuscript. Lingjing Lu, Yu Zhou, and Min Hu collected the references and drafted the manuscript. Juan Li and Hongxia Ma revised the manuscript. All authors have read and approved the final version of the manuscript.

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