

# **Efficacy of the Kampo Medicine Xiong-Gui-Jiao-Ai-Tang, a Traditional Herbal Medicine, in the Treatment of Threatened Abortion in Early Pregnancy**

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**Abstract:** This study was carried out to evaluate the clinical efficacy of Xiong-gui-jiao-ai-tang (Kyuki-kyogai-to), a traditional Chinese herbal medicine, in the treatment of threatened abortion in early pregnancy. We enrolled 72 women diagnosed with threatened abortion at Osaka Medical College Hospital and assigned them at random to the following two groups: a group of 36 women who received Xiong-gui-jiao-ai-tang at a dose of 7.5 g/day and another group of 36 women who received human chorionic gonadotropin (hCG) (control group). We found that in the Xiong-gui-jiao-ai-tang group ( $2.9 \pm 3.5$  days), the number of days required before hemostasis was reached in the uterus was significantly shorter than in the control group ( $10.8 \pm 8.2$  days,  $p < 0.0001$ ). Furthermore, the number of days required for retroplacental hematoma in the vicinity of the gestational sac to disappear was significantly shorter in the Xiong-gui-jiao-ai-tang group ( $9.9 \pm 7.1$  days) than in the control group ( $23.2 \pm 12.8$  days) ( $p < 0.0001$ ). In retroplacental hematoma size, significant rates of reduction were obtained in both major and minor axis measurements at the 7th day of treatment for the Xiong-gui-jiao-ai-tang group compared to the control group (control vs Xiong-gui-jiao-ai-tang: major axis:  $7.5 \pm 3.8\%$  vs  $42.3 \pm 10.5\%$ ; minor axis:  $15.3 \pm 16.8\%$  vs  $71.5 \pm 48.2\%$ ) ( $p < 0.0001$ , each case). The results of this study demonstrated the beneficial effects of Xiong-gui-jiao-ai-tang in stabilizing early pregnancy.

Xiong-gui-jiao-ai-tang can be expected to improve unstable early pregnancy with uterine bleeding and to prevent abortion.

*Keywords:* Xiong-Gui-Jiao-Ai-Tang (Kyuki-kyogai-to); Herbal Medicine; Retroplacental Hematoma; Threatened Abortion; Uterine Bleeding.

## Introduction

Threatened abortion has been an important condition in obstetric healthcare since ancient times. Vaginal bleeding in early pregnancy is the most common cause of reproductive failure. It may occur in up to 16% of pregnancies (Batzofin *et al.*, 1984) and is the most common cause of emergency hospital admission for women of reproductive age. In many cases, no apparent fetal or maternal cause of spontaneous abortion can be found (Suvonnakote, 1986; Harrison, 1993). It appears that separation of the early placenta, which results in the formation of retroplacental hematoma, plays an important role in bleeding which may subsequently affect fetal growth. Chromosome defects may be detected in over 50% of spontaneous abortion material (Lauritsen, 1972). This suggests abortion is nature's way of dealing with an error in human reproduction and therefore not worthy of medical interference (Vlaanderen and Treffers, 1987). However, spontaneous abortion invariably gives rise to pronounced physical and emotional traumatic responses (Kaij *et al.*, 1969). Such an approach may therefore not be appreciated by the couples concerned, and more active treatment may be expected and even demanded.

Human chorionic gonadotropin (hCG) and progestogen have been reported to yield beneficial long-term clinical results in the treatment of threatened abortion (Suvonnakote, 1986; Harrison, 1993; Toth, 2001; Palagiano *et al.*, 2004). Ou *et al.* (2001) demonstrated the usefulness of early antibiotic therapy in preventing loss of pregnancy in women with threatened abortion early in the first trimester in a 6-year retrospective study. Traditional Chinese (Kampo) medicines have been developed over a period of 3,000 years. However, because of its obscure theoretical basis, Kampo medicine has not gained the approval of the Western medical community (Xiu, 1988; Ushiroyama, 2004; Ushiroyama, 2005a; 2005b). On the other hand, Jiang *et al.* (1997) reported the efficacy of Chinese herbs in maintaining early pregnancy by the method of blood activation and stasis removal in accordance with diagnostic typing (qi stagnation, qi deficiency, cold condensation, and heat accumulation) in a clinical trial of Oriental medicine. However, the effectiveness of traditional herbal medicines has yet to be sufficiently studied.

The Chinese herbal medicine Xiong-gui-jiao-ai-tang (Kyuki-kyogai-to) has been used for the treatment of pathological bleeding from the uterine cavity, anus, and urinary tract. In Oriental medicine, Xiong-gui-jiao-ai-tang is also known as Jiao-ai-si-wu-tang and is a formulation with blood tonic effect. In Jin Gui Yao Lue, one of the classic textbooks of Chinese herbal medicine, it is noted that "application of this preparation is prescribed when a woman is pregnant and bleeding protractedly". It is also used "for abdominal pain during pregnancy". These descriptions suggest that threatened abortion is clinically indicated for

treatment with Xiong-gui-jiao-ai-tang. What remains after removal of the gelatin, mugwort leaf, and roasted glycyrrhia root from this preparation became the Si-wu-tang bequeathed to later generations, which is used in the treatment of anemia. Thus, in Oriental countries, Xiong-gui-jiao-ai tang has long been used for treating threatened abortion with uterine bleeding. To our knowledge, however, no report on the results of its clinical use in this regard has been published in any countries.

Along with Xiong-gui-jiao-ai-tang, Dang-gui-shao-yao-san is also an often used conventional Chinese herbal treatment for threatened abortion. However, it is noted in the provisions for Dang-gui-shao-yao-san that “it is indicated in cases in which pregnant women feel pain as though their abdominal region is being pulled”, and there is no mention of uterine bleeding. Accordingly, in the treatment of threatened abortion in Chinese medicine, Xiong-gui-jiao-ai-tang has been used in cases accompanying uterine bleeding and Dang-gui-shao-yao-san has been used if there has been abdominal pain alone. However, it remains unclear why the use of these drugs has been differentiated in this fashion.

This study is the first attempt to test Xiong-gui-jiao-ai-tang (Kyuki-kyogai-to) as an abortion-inhibiting agent. The aims of this study were to investigate: 1) the clinical efficacy of Xiong-gui-jiao-ai-tang for threatened abortion with main complaint of uterine bleeding; and 2) the changes in retroplacental hematoma in the vicinity of the gestational sac using transvaginal ultrasonography in a controlled study with a human chorionic gonadotropin (hCG) administration group.

## Materials and Methods

### *Patients*

The subjects were a total of 72 women (mean age:  $30.8 \pm 3.8$  years, range: 23–37 years) who presented with uterine bleeding in early pregnancy. They were enrolled in the study after obtaining their fully informed consent. No patient had any diseases associated with

**Table 1. Baseline Characteristics of the Subjects**

Variable	Xiong-Gui-Jiao-Ai-Tang	hCG	Significance
No. of subjects	33	36	
Age (Year) (SD)	$30.9 \pm 3.6$	$30.4 \pm 3.7$	n.s.
Number of deliveries (SD)	$1.81 \pm 0.8$	$1.79 \pm 0.9$	n.s.
Gestational week (SD)	$6.51 \pm 1.7$	$7.00 \pm 2.4$	n.s.
Proportion of use of hemostat agent (%)	0	33.3 (12/36)	0.0019
Proportion of hospitalization (%)	30.3 (10/33)	86.1 (31/36)	0.015
Longer length of RPH (mm)	$20.1 \pm 13.1$	$20.0 \pm 9.3$	n.s.
Shorter length of RPH (mm)	$13.7 \pm 15.6$	$11.1 \pm 5.3$	n.s.

RPH: retroplacental hematoma.

malignancy, endocrinological and metabolic problems, inflammation, or any history of treatment for infertility prior to the study. Important characteristics of each patient were collected and tabulated as shown in Table 1. No differences were noted in age or background of pregnancy among the groups at baseline.

### *The Herbal Preparation*

Xiong-gui-jiao-ai-tang (Kyuki-kyogai-to) is composed of 7 herbal ingredients (Table 2). It is a combination of the following: 5 g of Rehmannia root (*di huang*), 4 g each of Peony root (*shao yao*), and Japanese Angelica root (*dang gui*), and 3 g each of Roasted Glycyrrhiza root (*zhi gan cao*), Cnidium rhizome (*chuang xiong*), Mugwort leaf (*ai te*), and Gelatin (*e jiao*). A mixture consisting of these chopped ingredients was extracted with 1 liter of hot water, condensed by boiling to 600 ml, then filtered and lyophilized to prepare a powder which was stored at 4°C as 4 g lots of Xiong-gui-jiao-ai-tang extract. Four grams of extract was transformed to 7.5 g of granular-type agent (with addition of 3.5 g of drug additive, i.e. lactose) as a commercial drug (TSUMURA & Co., Tokyo, Japan).

**Table 2. Components of Herbal Drugs in Xiong-Gui-Jiao-Ai-Tang**

Rehmannia root	5.0 g	Peony root	4.0 g
Japanese angelica root	4.0 g	Roasted Glycyrrhiza root	3.0 g
Cnidium rhizome	3.0 g	Mugwort leaf	3.0 g
Gelatin	3.0 g		

### *Protocol*

After giving fully informed consent, patients were randomly allocated to either of two groups (envelope method). Thirty-six patients received 7.5 g of extracted granules of Kampo preparation each day (2.5 g of the commercial preparation in 100 ml of hot water taken about 30 minutes before every meal) for 8 weeks. For the remaining 36 patients, the fixed dose of 5,000 IU of human chorionic gonadotropin (hCG) was given intramuscularly 3 times a week. A hemostatic agent was also administered as required. Specific Kampo examinations (inspection, the listening and smelling, inquiry, and palpation: (four examinations in all) were not carried out in this study. Neither was the eight-principle pattern identification, the process of determining optimum patient status, considered in treatment with Xiong-gui-jiao-ai-tang. Three patients in the Xiong-gui-jiao-ai-tang group dropped out of the study by the second day of administration, leaving a total of 69 patients as the final total for the study (hCG group: 36 patients; Xiong-gui-jiao-ai-tang group: 33 patients).

Ultrasonographic studies were performed at the beginning of and after 7-day administration of Xiong-gui-jiao-ai-tang. For retroplacental hematoma around the gestational sac, we measured the major axis and minor axis of the part with the greatest

diameter. The same section of the uterus containing the longest major axis of the retroplacental hematoma was scanned at the same angle, to the extent possible, and time courses of change in size were compared.

### Data Analysis

Results are expressed as mean  $\pm$  SD. Statistical analysis was performed using the Wilcoxon signed-rank test for intergroup and intragroup comparisons, and the chi-square test to compare proportions.  $p < 0.05$  were considered significant.

### Results

There was no significant difference in the rate of miscarriage over the course of treatment between the Xiong-gui-jiao-ai-tang group (15.2%: 5/33) and the hCG group (19.4%: 7/36). The number of days required until hemostasis was significantly shorter in the Xiong-gui-jiao-ai-tang group ( $2.9 \pm 3.5$  days) than in the hCG group ( $10.8 \pm 8.2$  days) ( $p < 0.0001$ ). Furthermore, the number of days required for the retroplacental hematoma to disappear was also significantly shorter in the Xiong-gui-jiao-ai-tang group ( $9.9 \pm 7.1$  days) than in the hCG group ( $23.2 \pm 12.8$  days,  $p < 0.0001$ , Fig. 1). In retroplacental hematoma size, significant rates of reduction were obtained in major axis and minor axis measurements by the 7th day of treatment in the Xiong-gui-jiao-ai-tang group compared to the hCG group (hCG vs Xiong-gui-jiao-ai-tang: major axis:  $7.5 \pm 3.8\%$  vs  $42.3 \pm 10.5\%$ ; minor axis:  $15.3 \pm 16.8\%$  vs  $71.5 \pm 48.2\%$ ,  $p < 0.0001$ , Fig. 2).

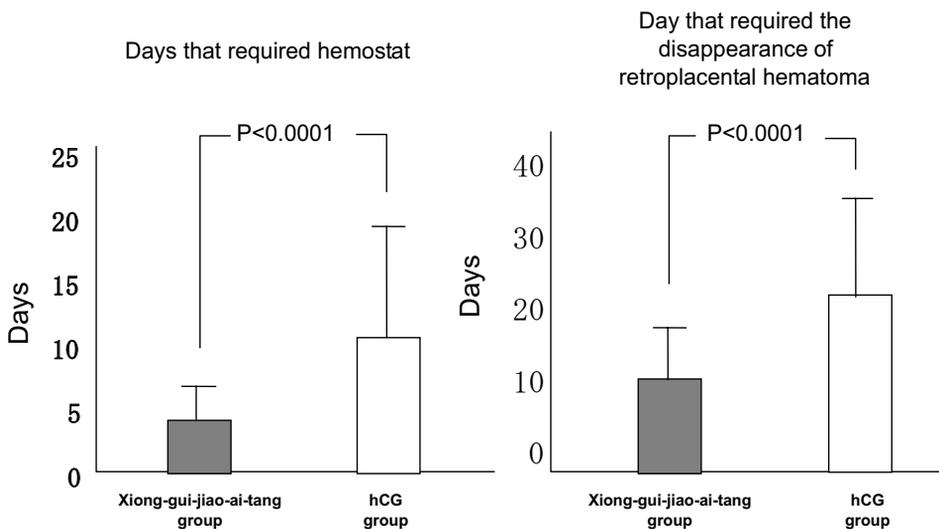


Figure 1. Comparison of number of days required for hemostasis of uterine bleeding and disappearance of retroplacental hematoma in the Xiong-gui-jiao-ai-tang and hCG groups.

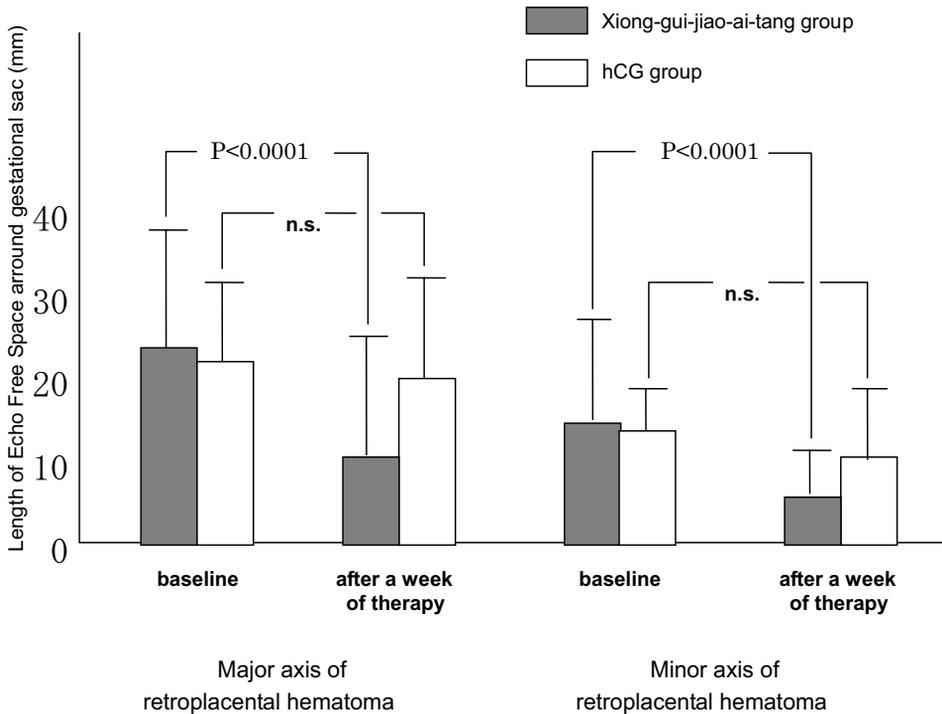


Figure 2. Comparison of changes in size of retroplacental hematoma in the Xiong-gui-jiao-ai-tang and hCG groups.

Two women who received treatment with Xiong-gui-jiao-ai-tang for uterine bleeding in the first trimester of pregnancy will be presented below. Figure 3 shows the features on transvaginal ultrasound examination in these women before and one week after the start of treatment. The upper column shows the findings from a 32-year-old woman who consulted our department because of bleeding in the 8th week of pregnancy. On sagittal view, a large retroplacental hematoma (29 x 8.1 mm) was visible around the gestational sac. This woman stayed in bed at home for one week while receiving Xiong-gui-jiao-ai-tang. Imaging conducted 7 days later revealed reduction of the retroplacental hematoma to 12 x 5.9 mm on sagittal view. The hematoma was no longer visible 7 days later. The lower column shows the findings for a 30-year-old woman who consulted our department with chief complaints of amenorrhea and small amounts of bleeding and was diagnosed with threatened abortion (at a gestational age of 5 weeks). Transvaginal ultrasound examination revealed retroplacental hematoma around the gestational sac on sagittal view. The hematoma had dimensions of 14 x 13 mm, and was larger than the gestational sac (12.3 mm in diameter). This woman also received Xiong-gui-jiao-ai-tang therapy and was instructed to stay in bed at home for one week. When the woman visited our department 7 days later, the retroplacental hematoma was no longer visible, and the gestational sac was larger than before (20.2 mm in diameter). Cardiac beats of the fetus were confirmed

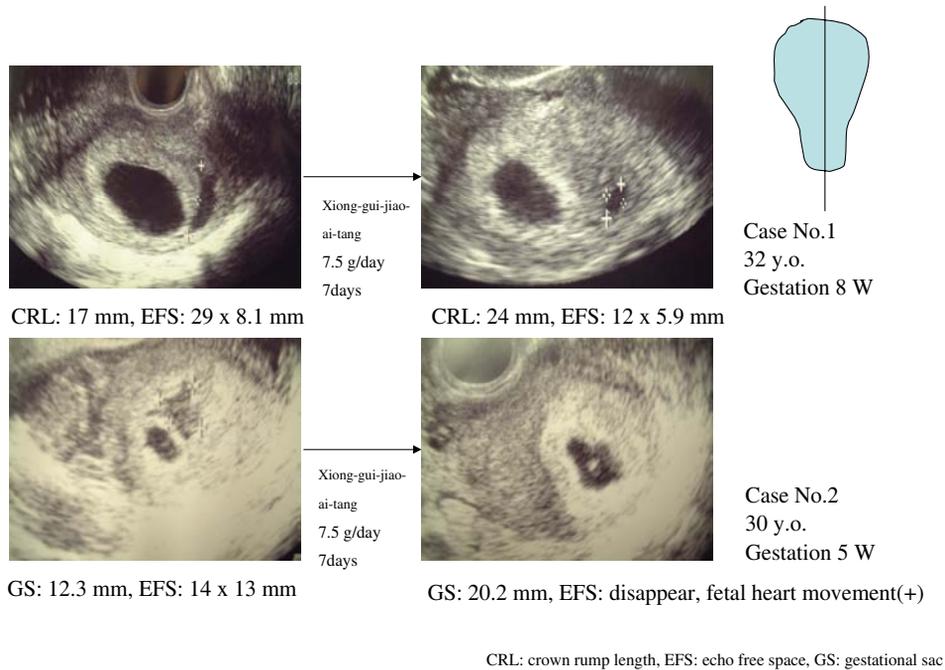


Figure 3. Change in ultrasonographic images in patients treated with Xiong-gui-jiao-ai-tang for one week.

at that time. Both women received Xiong-gui-giao-ai-tang prescription for another week after the disappearance of the retroplacental hematoma. The drug was then discontinued. The subsequent course of pregnancy was uneventful in both cases.

## Discussion

Clinical assessment of threatened abortion by history and physical examination is unreliable in most cases. Mild to moderate blood loss without loss of material and pain are clinical signs and symptoms characterizing threatened abortion. Diagnostic accuracy is improved by the addition of transvaginal sonography (Yip, 2003). Pain, fetal bradycardia, and fetal tachycardia do not appear to predict loss of pregnancy (Tannirandom, *et al.*, 2003). The presence of uterine subchorionic and retroplacental hematomas during the first trimester identifies a population of patients at increased risk of adverse pregnancy outcome (Nagy *et al.*, 2003). Intrauterine hematomas are commonly observed features on ultrasound examinations, especially among patients with clinically evident bleeding in early pregnancy. It has been suggested that a localized accumulation of blood causes mechanical uterine irritation and therefore stimulates contractions of uterine muscle (Tower and Regan, 2001). The incidence of first-trimester hematomas in patients with singleton intrauterine pregnancies diagnosed by ultrasound has been reported to be 3.1% (Nagy *et al.*, 2003). Nagy *et al.* (2003) reported that 18.7% of patients with intrauterine

hematomas subsequently had pregnancy loss at less than 24 weeks, although 9.5% of patients without intrauterine hematomas spontaneously aborted.

Placebo-controlled studies have reported that progestogen administration reduced the frequency of uterine contraction and abdominal pain (Palagiano *et al.*, 2004). Recent studies have also revealed the efficacy of exogenous hCG administration in continuing pregnancy and enhancing long-term clinical results for women with early threatened abortion (Harrison, 1993; Toth, 2001).

The classical therapeutic medications for uterine bleeding and lower abdominal pain during pregnancy diagnosed as threatened abortion are Xiong-gui-jiao-ai-tang and Dan-gui-shao-yao-san. Since ancient times, Dan-gui-shao-yao-san seems to have been frequently used in Chinese medicine to stabilize pregnancy in the presence of abdominal pain. Among the components of Dan-gui-shao-yao-san, are Japanese angelica root (*dang gui*), Peony root (*shao yao*), Cnidium rhizome (*chuan xiong*), and Atractylodes rhizome (*bai shu*) which work together to improve blood deficiency and Yin deficiency. According to its description, Xiong-gui-jiao-ai-tang is used mainly when uterine bleeding is observed. This formulation has Japanese angelica root (*dang gui*), Peony root (*shao yao*), and Cnidium rhizome (*chuan xiong*) in common with Dan-gui-shao-yao-san, with the addition of Gelatin (*e jiao*) and Mugwort leaf (*ai te*), both of which are effective as hemostatic agents. It may be that because of this, the Xiong-gui-jiao-ai-tang formulation has a hemostatic effect in addition to its embryo stabilizing effect. However, to our knowledge, there have been no reports of clinical studies comparing the efficacy of the Xiong-gui-jiao-ai-tang herbal preparation with that of drugs used in modern Western medicine such as hCG and antibiotics for the treatment of threatened abortion in humans.

In the present study, we demonstrated that Xiong-gui-jiao-ai-tang is effective in shortening the number of days required for the reduction of retroplacental hematoma and the hemostasis of uterine bleeding in patients with threatened abortion. Moreover, compared to hCG, which has been widely used for a long period of time in the treatment of threatened abortion, the numbers of days required for disappearance of retroplacental hematoma and hemostasis of uterine bleeding have been shortened by about 1/2 and 1/4, respectively. Early adhesion to the lapsed intermembrane space, mainly due to the blood-producing and hemostatic effects of Gelatin (*e jiao*), can be considered one of the reasons why Xiong-gui-jiao-ai-tang has since ancient times been used in the treatment of threatened abortion with uterine bleeding but without abdominal pain. It is thought that the addition of the anemia-improving effect of Japanese angelica root and the tocolytic effect of peony root restores the oxygen supply to the embryo.

As illustrated above, the efficacy of Xiong-gui-jiao-ai-tang in stimulating early reduction of retroplacental hematoma and alleviating threatened abortion seems to be primarily due to the early adhesion to the lapsed intermembrane space, largely the effects of the gelatin (*e jiao*) and the Japanese angelica root. It also appears possible that Xiong-gui-jiao-ai-tang has inhibitory effects on uterine contraction, involving PGF2 $\alpha$  or oxytocin, as is the case with Goshitsu-san, another herbal medicine (Fukushima *et al.*, 1994). Chimura (1989) investigated the effects of Dang-gui-shao-yao-san and some of its components, Japanese angelica root, Peony root, and Cnidium rhizome, on spontaneous uterine contractile waves.

Although marked changes in contractile patterns were not observed with the individual components, a contraction-inhibiting effect was found with 1mg/ml Dang-gui-shao-yao-san. Xiong-gui-jiao-ai-tang also contains Japanese angelica root, Peony root, and Cnidium rhizome. The tocolytic effects of these herbs may thus restore the oxygen supply to the embryo. At present, nothing more definite can be said concerning the mechanism of action of Xiong-gui-jiao-ai-tang in improving unstable early pregnancy. Additional studies are needed for full elucidation of this mechanism.

Nagy *et al.* (2003) demonstrated that intrauterine hematoma identifies a gestation at risk for a number of complications including preeclampsia, pregnancy-induced hypertension, fetal growth restriction, preterm delivery, and placental abnormalities. Furthermore, they found a 5.8-fold increased risk of placental abruption in patients with retroplacental hematomas compared to the control patients. Accordingly, the prompt restoration of placental tissue in early stage pregnancy by Xiong-gui-jiao-ai-tang not only stabilizes the pregnancy subsequently, but can also be expected to be effective in preventing a range of complications in the last stages of pregnancy.

In conclusion, Xiong-gui-jiao-ai-tang shortens the time required for hemostasis in cases of threatened abortion accompanied by uterine bleeding. It also promotes reductions in the size of retroplacental hematoma and shortens the number of days required for its disappearance. This suggests the possibility that this preparation is clinically useful in the treatment of threatened abortion. In addition to improving blood deficiency, this preparation promotes hemostasis, due to its inclusion of Mugwort leaf (*ai te*) and Gelatin (*e jiao*), however, the mechanism by which it promotes the disappearance of retroplacental hematoma requires further study.

## References

- Batzofin, J., W. Fielding and E. Freedman. Effect of vaginal bleeding in early pregnancy on outcome. *Obstet. Gynecol.* 65: 515–518, 1984.
- Chimura, T. Effects of Toki-shakuyaku-san on keeping pregnancy. *Rec. Preg. Kampo Med. Obstet. Gynecol.* 6: 67–72, 1989. (in Japanese)
- Fukushima, M., K. Yoshizawa, M. Kushibiki and M. Sugawara. Inhibitory effect of Goshitsu-san on myometrial contraction in rats. *J. Trad. Med.* 11: 65–69, 1994.
- Harrison, R.F. A comparative study of human chorionic gonadotropin, placebo, and bed rest for women with early threatened abortion. *Int. J. Fertil. Menop. Studies* 38: 160–165, 1993.
- Jiang, J., G. Li and M. Zang. Clinical observation on 41 cases of threatened and habitual abortion treated by blood activation and stasis removal. *J. Trad. Chin. Med.* 17: 259–265, 1997.
- Kaij, L., A. Malmquist and A. Nilsson. Psychiatric aspects of spontaneous abortion. The importance of bereavement attachment and neurosis in early life. *J. Psychosom. Res.* 13: 53–62, 1969.
- Lauritsen, J.G. Etiology of spontaneous abortion. A cytogenetic and epidemiological study of 288 abortuses and their parents. *Acta Obstet. Gynaecol. Scand.* 52: 1–59, 1972.
- Nagy, S., M. Bush, J. Stone, R.H. Lapinski and S. Gardo. Clinical significance of subchorionic and retroplacental hematomas detected in the first trimester of pregnancy. *Obstet. Gynecol.* 102: 94–100, 2003.

- Ou, M.C., C.C. Pang, F.M. Chen, C.H. Su and D. Ou. Antibiotic treatment for threatened abortion during the early first trimester in women with previous spontaneous abortion. *Acta Obstet. Gynecol. Scand.* 80: 753–756, 2001.
- Palagianò, A., C. Bulletti, M.C. Pace, D. De Ziegler, E. Cicinelli and A. Izzo. Effects of vaginal progesterone on pain and uterine contractility in patients with threatened abortion before twelve weeks of pregnancy. *Ann. New York Acad. Sci.* 1034: 200–210, 2004.
- Suvonnakote, T. Treatment of threatened abortion with human chorionic gonadotropin. *J. Med. Assoc. Thai* 69: 654–658, 1986.
- Tannirandorn, Y., S. Sangsawang and S. Manotaya. Fetal loss in threatened abortion after embryonic/fetal heart activity. *J. Gynecol. Obstet.* 81: 263–266, 2003.
- Toth, P. Clinical data supporting the importance of vascular LH/hCG receptors of uterine blood vessels. *Sem. Reprod. Med.* 19: 55–61, 2001.
- Tower, C.L. and L. Regan. Intrauterine haematomas in a recurrent miscarriage population. *Hum. Reprod.* 16: 2005–2007, 2001.
- Ushiroyama, T. Proposal of practicing Japanese Kampo in menopausal medicine. *J. Psychosom. Obstet. Gynecol.* 26: 5–7, 2004.
- Ushiroyama, T. Japanese Kampo medicine for women: historical perspectives of Koho-ha school and current concerns in menopausal medicine. *Adv. Obstet. Gynecol.* 57: 131–150, 2005a.
- Ushiroyama, T. Kampo medicine may be required for the treatment of human diseases. *Evol. Kampo* 1: 2–3, 2005b.
- Vlaanderen, W and P.E. Treffers. Prognosis of subsequent pregnancies after recurrent abortion in first trimester. *Br. Med. J.* 33: 471–474, 1987.
- Xiu, R.J. Microcirculation and traditional Chinese medicine. *JAMA* 260: 1755–1757, 1988.
- Yip, S.K., D. Sahota and L.P. Cheung. Accuracy of clinical diagnostic methods of threatened abortion. *Gynecol. Obstet. Invest.* 56: 38–42, 2003.

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