

## Kampo Medicine - Current Research

*Clinical Experience for Functional Sterility, Complicated with Irregular Menstruation and Anovulatory Cycle, Administrated of Saireito*

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### [Abstract]

Kampo therapy for sterility is often used as single or adjunctive agent medicated with a western medicine, for primarily treating the functional abnormalities such as anovulation. Typically, the chief patterns of administration are *tokishakuyakusan*, *unkeito*, and other agents that improve blood deficiency. Many researches have been reported concerning their efficacy in treatment of sterility. In recent years, however, many patterns other than the type of blood deficiency may be present due to food satiation and the stress-related disease. Thus, newer approaches of Kampo therapy adapted for the modern age would be necessary for the treatment of sterility.

Therefore, we tried administrating *saireito*, a formulation to treat Qi stagnation and fluid retention, for patients with sterility complicated with irregular menstruation or anovulatory cycle. Its excellent efficacy was demonstrated by assessment of changes in sex hormonal levels, the recovery rate of menstrual cycle, and the rates of ovulation and pregnancy before and after the oral administration. Since *saireito* has ever exerted the alleviating effect on stress in some cases in addition to the improving effect on ovarian function, it is estimated to be an effective administration for patients with sterility accompanied with the menstrual irregularity or the anovulatory cycle.

**Key words:** Primary Sterility, Saireito, Irregular Menstruation, Anovulatory Cycle

### [Introduction]

*Saireito* is a combination formula made up of *shosaikoto* and *goreisan* for the treatment of stagnation of liver Qi and fluid disturbance. It is supposed to have endogenous steroid hormone-like actions and inhibits platelet aggregation and its effects for the treatment of gestational edema and habitual abortion have been confirmed in the field of obstetrics and gynecology. Recently it has reportedly shown to be effective for polycystic ovary syndrome and is therefore expected to be an effective therapeutic drug for the treatment of abnormal endocrine metabolism.

In infertility patients, the presence of "Qi" disorder like Qi depression or Qi stagnation has been pointed out. Moreover, the metabolic syndrome has developed into a social problem, so there are not many cases which blood deficiency is the predominantly major. Therefore, we tried *saireito* in patients with functional sterility complicated by irregularities of menstruation or ovulation disorders. We examined variations in female hormone concentrations, menstrual cycle, variations in ovulation ratio and the occurrence of pregnancies associated with the internal use of *saireito* to determine whether *saireito* is an effective drug for the treatment of infertility.

### [Methods]

During the period from January 2008 until December 2011, we prescribed *saireito* extract granules (Kracie) 8.1 g/bid before the meals after obtaining a sufficient informed consent for 24 (average age 34.7±4.5 years) out of 89 patients who visited our clinic with the desire to have children and presented with irregular menstruation like oligomenorrhea or amenorrhea and were diagnosed to suffer from ovulation disorders or functional sterility. Patients with organic factors like myoma uteri or the like female factors or else male factors were excluded. Each individual patient underwent oriental medical examinations to establish the disease pattern that were subsequently analyzed, but prescribed *saireito* regardless of the pattern. For this reason the formula may possibly have been administered for off-label use. The ethics committee of our clinic discussed the issue and approved, that in

cases of apparent deviation from the pattern patients in question were excluded from the study. Blood examinations were performed before the administration, 4 and then 8 weeks later between the 5<sup>th</sup> to 7<sup>th</sup> day after onset of the menstruation and the variations in the measured LH, FSH, LH/FSH, testosterone values examined. Also, any variations in the menstrual cycle and the occurrence of ovulations before and after the administration of *saireito* were confirmed with reference to the basal body temperature. Establishment of pregnancies was later confirmed by the delivery.

The occurrence of adverse events related to the internal use was also investigated. We attempted at the same time also to make a comparative study pertaining to Qi, Blood and Water including all infertility patients, those treated with *saireito* as well as the patients in whom pregnancies occurred after treatment with *saireito*.

#### [Results]

The 24 infertility patients presenting with irregular menstruation were treated with *saireito*. In 15 of these patients a recovery of the menstrual cycle could be observed (menstrual cycle improvement ratio 63%). Also, based on the basal body temperature ovulations were observed in 14 of the patients with anovulatory cycles and among these ovulation was definitely established in 9 patients (ovulation ratio 64%).

Table 1: List of patients who became pregnant

	Age	BMI	Gravidity	Parity	Abortion	Menstrual cycle (before)	Menstrual cycle (after)	Ovulation (before)	Ovulation (after)	Duration until pregnancy (Cycle)	PCOS
1	33	26.6	1	1	0	Oligomenorrhea	Normal	No	Yes	4	No
2	28	17.5	1	0	0	Oligomenorrhea	Normal	No	Yes	3	Yes
3	34	19.9	0	0	0	Oligomenorrhea	Normal	Yes	Yes	2	No
4	34	20.1	0	0	0	Oligomenorrhea	Normal	No	Yes	4	No
5	42	28.4	2	1	1	Oligomenorrhea	Normal	No	Yes	3	No
6	33	22.6	0	0	0	Oligomenorrhea	Normal	Yes	Yes	6	No
7	40	21.1	5	1	3	Oligomenorrhea	Normal	Yes	Yes	7	No
8	31	21.8	1	1	3	Oligomenorrhea	Normal	No	Yes	2	No
9	24	20.7	1	1	1	Oligomenorrhea	Normal	Yes	Yes	6	No
10	32	18	0	0	0	Oligomenorrhea	Normal	No	Yes	5	Yes
11	34	23.6	0	0	0	Oligomenorrhea	Normal	Yes	Yes	4	No
12	34	19.3	0	0	0	Oligomenorrhea	Oligomenorrhea	Yes	Yes	6	Yes
13	37	17.4	0	0	0	Oligomenorrhea	Oligomenorrhea	No	Yes	12	No
14	40	24.9	0	0	0	Oligomenorrhea	Oligomenorrhea	No	Yes	4	No
15	37	21	2	1	1	Oligomenorrhea	Normal	Yes	Yes	3	No
16	39	39	2	2	0	Oligomenorrhea	Normal	Yes	Yes	7	No

Among the 24 infertility patients pregnancies occurred following treatment with *saireito* in 16 women (pregnancy rate 67%, see Table 1).

Treatment duration with *saireito* until establishment of pregnancies was on the average  $4.9 \pm 2.5$  weeks. Moreover, while 6 out of the 24 patients were diagnosed with Polycystic Ovary Syndrome (PCOS), pregnancies occurred in 3 of those patients (pregnancy ratio 50%). A breakdown of the outcome in the 16 women who got pregnant showed ongoing pregnancies in 14 (87%) women and spontaneous abortion in 2 (13%). The delivery in those women, who actually gave birth was uneventful for both mother and child, considered to be also due to the fact, that the children had simultaneously been medicated and obvious anomalies were not observed.

Regarding fluctuations in the gonadotrophic hormone levels the LH values before, 4 and 8 weeks respectively after the administration were  $7.1 \pm 4.8$ ,  $5.5 \pm 2.8$  and  $4.7 \pm 1.1$  mIU/ml. While the LH concentration tended to be both before and after the administration low, significant differences were not observed. The LH/FSH ratio was  $0.88 \pm 0.62$ ,  $0.62 \pm 0.27$  and  $0.55 \pm 0.13$  respectively and decreased significantly before and after the administration. ( $P < 0.05$ ). No significant differences were observed in FSH and testosterone levels (Figure 1).

Adverse events associated with the internal use included the occurrence of mild diarrhea, vomiting and similar symptoms of gastroenteritis in one patient (4.2%), but these were alleviated by discontinuing the medication. Otherwise, including clinical laboratory tests, no problematic side effects were observed.

Examination of Qi, Blood and Water during the visits of the 89 infertility patients showed Qi deficiency in 31 cases (35%), Qi stagnation in 39 (44%), Blood deficiency in 50 (56%), Blood stagnation in 31 (35%) and Water stagnation in 26 (29%) patients. Regarding the 24 patients treated with *saireito* 9 (38%) presented with Qi deficiency, 10 (42%) with Qi stagnation, 13 (54%) Blood deficiency, 10 (42%) Blood stagnation and 8 (50%) with Water stagnation. Among the 16 women in whom a pregnancy occurred 6 (38%) presented with Qi deficiency, 6 (38%) with Qi stagnation, 8 (50%) Blood deficiency, 7 (44%) Blood stagnation and 7 (44%) with Water stagnation (Table 2).

Table 2: Patterns in infertility patients and patients treated with *saireito*

	Qi deficiency	Qi stagnation	Blood deficiency	Blood stagnation	Water stagnation
All infertility patients (89 patients)	31/89 (35%)	39/89 (44%)	50/89 (56%)	31/89 (35%)	26/89 (29%)
Patients treated with <i>saireito</i> (24 patients)	9/24 (38%)	10/24 (42%)	13/24 (54%)	10/24 (42%)	8/16 (50%)
Patients treated with <i>saireito</i> in whom a pregnancy occurred	6/16 (38%)	8/16 (50%)	8/16 (50%)	7/16 (44%)	7/16 (44%)

[Discussion]

The factors responsible for female infertility can broadly be classified into functional and organic disorders. Disorders of tubal patency, intrauterine disorders, peritubal adhesion, myoma uteri, endometriosis etc. can be mentioned as organic

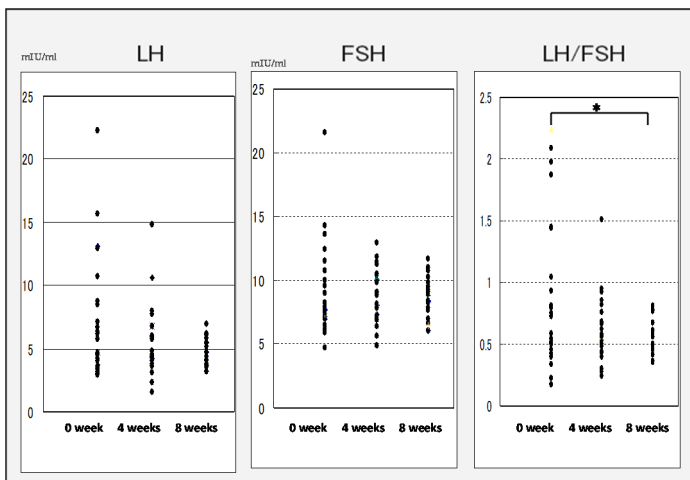
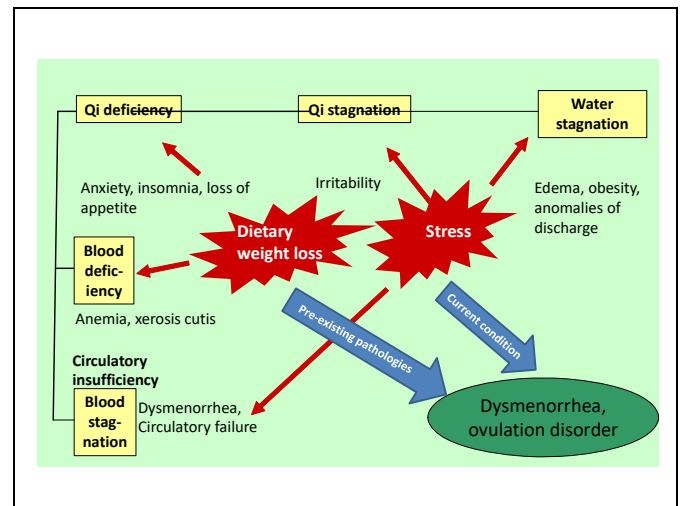


Figure 1: Fluctuations in hypophyseal hormones associated with the administration of *saireito*

anomalies, but the progress in assisted reproductive technology (ART) and fiberoptic surgery have led to remarkable improvements in therapeutic results<sup>1)</sup>. While progress in recombinant preparations and gonadotropin therapies allowed to achieve higher ovulation ratios in cases of functional anomalies, the pregnancy ratio has not markedly changed and conditions like ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies cannot be avoided. The results of infertility treatment have improved remarkably, but there are still some infertility patients whose cause is unknown, and even if the infertility treatment with ART is performed, there are many patients who have difficulty getting pregnant because of infertility<sup>2)</sup>. Among oriental medical concepts regarding infertility the "kidneys" are thought to control reproduction, so that the condition is considered to be based on menstrual anomalies due to "kidney deficiency"<sup>2)</sup>. However, the condition is often influenced by multiple factors like anemia and chilling correlated to "Blood deficiency", "Blood stagnation" caused by circulatory insufficiency, stress-induced mental conditions like "liver depression and Qi stagnation", "disorders of the body's fluid metabolism" due to disorders of pelvic blood flow etc., which often are present in various combinations (Figure 2). Some reports state, that abdominal or tongue examinations showed in actual clinical practice a close correlation of liver depression and Qi stagnation, "Blood stagnation" and "disorders of the body's fluid metabolism" with infertility, so that *Bupleurum* preparations or drugs for overcoming Blood stagnation are effective<sup>2)</sup>. Regarding the "pattern" of infertility a study conducted in 1989 showed that approximately 65% of the cases presented with a deficiency pattern, while excess patterns were reportedly found in less than 10%. Regarding anomalies of Qi, Blood and Water "Qi deficiency" was reported found in 32%, "Qi stagnation" in 37%, "Blood deficiency" in 61% and "Blood stagnation" in 22% respectively<sup>3)</sup>. For this reason formulas for the treatment of "Blood deficiency": *Tokishakuyakusan* and *unkeito* were frequently chosen and there are multiple reports on their effects in the treatment of infertility<sup>4,5)</sup>.

Figure 2: Pathology in modern infertility patients (personal proposal)



*Saireito* is a combination formula composed of *shosaikoto* and *goreisan* that includes 12 crude drugs and is designed to alleviate stagnation of liver Qi and disorders of the body's fluid disturbance. The original text in the "Shi yi de xiao fang 世医得效方" (Effective Formulas from Generations of Physicians " by Wei Yi - Lin (危亦林 1277-1347) says "very effective for curing wind damage, summerheat damage and malaria" and the formula was mainly used for conditions associated with inflammation. Asada Sohaku's text "Futsugo Yakushitsu Hokan" contains the passage: "This formula is used for people with a *shosaikoto* pattern to alleviate feelings of distress accompanied by excessive thirst combined with diarrhea. It is particularly effective for summerheat epidemics.", describing the symptoms of the *shosaikoto* pattern. Main indications are nephrotic syndrome, chronic nephritis and similar renal diseases, chronic hepatitis etc. where a mild degree of edema is observed, heat stroke and the like acute forms of enteritis, exudative otitis media, habitual headache as well as a combination with steroid hormones (to reduce dose or alleviate side effects). Regarding the mechanism of action it has been reported to stimulate the hypothalamus – hypophysis – adrenal system, while *Glycyrrhizae Radix* inhibits the cholesterol metabolism in the liver and reportedly increases steroid production<sup>6)</sup>. In the field of obstetrics and gynecology *saireito* is used for the gestational

edema associated with habitual abortion, and used especially often during pregnancy. *Saireito* administered as a treatment of habitual abortion has been reported to be safe for the fetus even during fetal organ period<sup>7</sup>. It is therefore presumed to be one of safe therapeutic drugs for patients desiring to have children. Recently multiple reports describing cases in which pregnancies have been established through treatment with *saireito* have been published<sup>8,9</sup>. We therefore conducted this study based on the assumption, that *saireito* is an effective formula for the treatment of infertility.

When 24 patients complaining of infertility associated with menstrual irregularities were treated with *saireito*, pregnancies were established in 16 of these patients (67%) within a period of  $4.9 \pm 2.5$  weeks. In 9 (64%) out of 14 patients in whom anovulatory cycles were observed, ovulations were confirmed based on the basal body temperature. In former reports about Kampo treatment for infertility *tokishakuyakusan* led to an ovulation ratio of 44% and a pregnancy ratio of 22%, while *Unkeito* similarly led to an ovulation ratio of 50-60% and a pregnancy ratio of 18%<sup>10</sup>. Thus, compared to the aforementioned Blood deficiency improving formulas, *saireito* achieved even higher ovulation and pregnancy ratios. Comparing the levels of the gonadotrophic hormones before and after administration showed a decreasing tendency for LH values and moreover a decrease in the LH/FSH ratio ( $P < 0.05$ ). *Saireito* probably stabilizes the gonadotrophic hormone balance, thereby possibly enabling an effective action at hypophyseal hormone levels. Regarding PCOS the number of cases was few with only 6 patients, but in 3 (50%) of those a pregnancy was established. Thus, establishment of pregnancies was observed in a comparatively high number of cases treated with *saireito*.

Generally, clomifene citrate or gonadotropin preparations are used for in the field of infertility therapy as the therapeutic drug for the treatment of ovulatory disorders. Yet, since they might cause the development of OHSS besides their other effects, multiple pregnancies could develop in case of superovulation. For these reasons the benefits of Kampo therapy with its fewer side effects is currently

reconsidered. Some reports point out, that in modern society the pathology of infertility patients suggests a strong psychosomatic correlation, which bestows great importance on healing "Qi" anomalies with the Kampo therapy<sup>11</sup>. In particular "liver depression and Qi stagnation" and "disorders of the body's fluid metabolism" are frequently observed pattern in infertility patients, so that *saireito*, designed to heal stress or obesity seems to be indicated for the "pattern" of modern infertility patients. In practice Murata's report in 1989 found that 32% of the patterns were "Qi deficiency", 37% "Qi stagnation", 61% "Blood deficiency" and 22% "Blood stagnation"<sup>3</sup>, while the current study revealed 35% of the patterns to be "Qi deficiency", 44% "Qi stagnation", 56% "Blood deficiency" and 35% "Blood stagnation", indicating that the portion of "Qi stagnation" and "Blood stagnation" has increased as compared with former reports, which in turn is possibly correlated to the larger number of established pregnancies through treatment with *saireito*. Moreover, the effectiveness of *saireito* for the treatment of PCOS has recently also been confirmed<sup>12,13</sup>. PCOS is an endocrine disorder associated with irregularities of menstruation or polycystic ovaries, hyperandrogenemia or increased secretion of LH. The pathology suggests, based on the presence of obesity or insulin resistance, a correlation with the metabolic syndrome<sup>14</sup>. This may lead to ovulatory disorders and thus frequently be correlated to the pathology of infertility, so that *saireito* presumably is beneficial for infertility patients suffering from complication with PCOS.

It is well known that *tokishakuyakusan* or *unkeito* are used as Kampo therapy for infertility and their use is by now general practice. In recent years the nature of the infertility "pattern" is possibly changing, so that for infertility patients in whom these formulas do not lead to the establishment of pregnancies, a therapy based on Kampo diagnosis is adopted when it seems to be necessary to choose a more suitable formula. Verification of the effectiveness of *saireito* still needs further study, but for modern infertility patients and complicating menstruation irregularities or ovulatory disorders *saireito* can be considered to be one effective formula.

## [Conclusions]

The internal use of *Saireito* for the treatment of infertility complicated by menstruation irregularities or ovulatory disorders has led in many patients to a normalization of the menstrual cycle or the establishment of pregnancies. Apart from improving ovarian function, *saireito* also alleviates the stress associated with infertility treatment and is therefore considered a possibly effective formula for the treatment of infertility.

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