Effects of Switching to Wen-Jing-Tang (Unkei-To) from Preceding Herbal Preparations Selected by Eight-Principle Pattern Identification on Endocrinological Status and Ovulatory Induction in Women with Polycystic Ovary Syndrome

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Abstract: The objective of this study was to investigate the effects of switching therapy to Wen-jing-tang (Unkei-to) from previous selected herbal preparations on endocrine levels and induction of ovulation in women with polycystic ovary syndrome (PCOS). Sixty-four anovulatory women diagnosed with PCOS were enrolled in the study. After Kampo diagnosis, subjects received matched Kampo preparations (43 cases: Dang-gui-shao-yao-san, 21 cases: Gui-zhi-fu-ling-wan) selected by the matching theory of eight-principle pattern identification and Kampo diagnosis based on concepts of the qi, blood, and fluids as the physiologic activity. Fifty-four women who failed to ovulate after an 8-week treatment were randomly allocated to continuation of treatment with the preceding Kampo prescription (continuation group, n = 27) or treatment with Wen-jing-tang (switching group, n = 27). Plasma FSH, LH and estradiol levels were measured and ovulation rates were determined at the beginning and after an 8-week treatment with the preceding Kampo prescription, as well as after the subsequent 8-week treatment with the same preparation or Wen-jing-tang. No decrease in mean plasma LH level was observed in the 54 women who failed to ovulate among the 64 treated with a Kampo preparation. After the 8-week treatment with Wen-jing-tang, plasma LH levels were decreased by 58.2% (p < 0.0001) and 49.4% (p = 0.0005) in the groups switched from Dang-gui-shao-yao-san and Gui-zhi-fu-ling-wan, respectively. In the group switched from Dang-gui-shao-yao-san, a tendency towards increase in plasma estradiol level was observed (1.51-fold, p = 0.055), which was significant compared with that in the group switched from...
Gui-zhi-fu-ling-wan (p = 0.032). The ovulation rate with switching of treatment to Wen-jing-tang was significantly higher (59.3%) than that with continued use of the same preparation (7.4%, p = 0.0036).

This study confirmed that Wen-jing-tang was effective in improving endocrine condition in the treatment of disturbances of ovulation in patients with PCOS without taking eight-principle pattern identification into consideration. This finding indicates that Wen-jing-tang is appropriate for use in treating PCOS in women with various constitutions (as determined by the matching theory of eight-principle pattern identification) in clinical practice and may prove to be a potent therapeutic agent with a wide therapeutic spectrum.

Keywords: Wen-jing-tang (Unkei-to); Ovulatory Failure; Polycystic Ovary Syndrome; Endocrinological Change; Eight-Principle Pattern Identification.

Introduction

Herbal medicine has conventionally been used in the treatment of menstrual cycle abnormalities and unidentified climacteric complaints. Wen-jing-tang has been reported to exhibit clinical efficacy in the treatment of vaginal bleeding other than that due to menstruation, disturbance of ovulation and infertility (Ushiroyama et al., 1995, 2002 and 2003b; Ushiroyama, 2003). Polycystic ovary syndrome (PCOS) is a disease developing in women of relatively young age that begins with menstrual cycle abnormality and progresses to disturbance of ovulation and finally endocrine conditions such as amenorrhea accompanied by organic change of the ovary in the period of sexual maturation and infertility. It is the most common endocrine disorder in women of fertile age. Estimates of its prevalence vary between 3% and 20%, depending on the diagnostic criteria used and the population studied (Franks, 1995). A prevalence of 5%–17% has been reported for Caucasian women (Asuncion et al., 2000). Previously, primary treatment of PCOS involved ovarian drilling, possibly followed by ovarian induction with clomiphene citrate or gonadotropins (Farquhar et al., 2001). Ovarian drilling was hypothesized to decrease ovarian androgen production. Currently, the standard treatment for induction of ovulation in these patients is clomiphene citrate. The success rate with clomiphene citrate varies: 80% ovulation and 30%–40% pregnancy rates have been reported (Lunenfeld et al., 1991; Kousta et al., 1997; Imani et al., 1998 and 1999). Recently, research on the relationship between PCOS and insulin resistance has led to the use of insulin-sensitizing medications, such as metformin, for induction of ovulation (Nardo and Rai, 2001; Kocak et al., 2002; Kashyap et al., 2004; Vanky et al., 2004). However, despite widespread acceptance and zealous use of such medications, metformin has never been compared to clomiphene citrate in a direct randomized control trial. Though treatment with it has not been fully established, recent studies have revealed that Wen-jing-tang, an herbal drug, is effective in decreasing basal plasma LH level and that continuous administration of it increases ovulation rate (Ushiroyama et al., 2001; Ushiroyama, 2003).

In practical Kampo medicine, Kampo diagnosis, based on the concepts of the eight guiding (four paired) parameters of physical and psychological condition (Yin/Yang,
Exterior/Interior, Cold/Heat, and Hyper/Hypo-condition), has provided the basis for diagnosis and treatment (Wiseman and Ellis, 1996; Ushiroyama et al., 2005). The fundamental nature and location of disease is determined according to the eight principles. Patients have been treated with the theory of “treatment according to pattern identification” after obtaining patient and disease data through the four examinations (listening, smelling, inquiry, and palpation). This diagnostic process is unique to Kampo medicine and is not included in modern Western medicine (Ushiroyama, 2005). The eight principles are not mutually exclusive and unrelated; combinations, conversions, and complexes of them commonly occur (Wiseman and Ellis, 1996). It was reported that endocrinological changes and ovulation rate after treatment with Wen-jing-tang did not differ significantly between women with excess/repletion patterns and those with deficiency/vacuity patterns (Ushiroyama et al., 2003b). Thus, it is likely that certain types of Kampo preparations will exhibit sufficient efficacy, even if the theory of herbal medicine focusing on the traditional diagnosis of eight-principle pattern identification is not followed.

The aim of this randomized study was to determine whether Wen-jing-tang was effective in the treatment of anovulatory patients with PCOS who were not considered a target group of use of Wen-jing-tang based on the matching theory of eight-principle pattern identification.

Materials and Methods

Subjects

Sixty-four anovulatory women, aged 18–33 years (range: 23.8 ± 4.1 years), who were diagnosed with PCOS in our outpatient clinic between September 1993 and May 2004, were enrolled in the study. None of the subjects had received any hormonal treatment for at least 6 months before enrollment into the study. PCOS was diagnosed based on the following clinical findings:

1. Basal level of plasma LH >10 mIU/ml.
2. Plasma LH level over three-fold higher than plasma FSH level on LH-RH test.
3. Necklace sign on transvaginal echography.

Experimental Procedures

Appropriate Kampo prescription was selected using the matching theory of eight-principle pattern identification based on the concepts of the eight guiding (four paired) parameters of physical and psychological condition (Yin/Yang, Exterior/Interior, Cold/Heat, and Hyper/Hypo-condition) and also using Kampo diagnosis based on concepts of the qi, blood, and fluids as the physiological activity for the 64 women at the start of this study (Table 1). Based on Kampo diagnosis with SHO, Dang-gui-shao-yao-san and Gui-zhi-fu-ling-wan were prescribed in 43 and 21 cases, respectively, as Kampo preparations. They received 7.5 g of extracted granules of Kampo preparation (2.5 g of the commercial preparation
in 100 ml of hot water taken about 30 minutes before every meal) every day for 8 weeks. Fifty-four women did not ovulate after 8-week administration of the preceding Kampo prescription, which had been selected according to the eight-principle pattern identification and Kampo diagnosis. They were randomly allocated to either of two treatment groups (envelope method). In 27 cases, the preceding Kampo prescription (Dang-gui-shao-yao-san: 19 cases, Gui-zhi-fu-ling-wan: eight cases) was continued for another 8 weeks (continuation group). In the remaining 27 cases, the preceding Kampo prescription was switched to Wen-jing-tang for a subsequent 8-week therapy (switching group). Blood samples were obtained at the beginning and after 8-week administration of the initially chosen Kampo preparation and after the subsequent 8-week administration of Wen-jing-tang through an indwelling i.v. line at 10:00 hours for analyses of FSH, LH and estradiol.

**Hormone Assays**

Plasma FSH, LH and estradiol concentrations were measured by an established evanescent wave immuno-luminescent method with a commercial kit (Evanet 20, Nissui Pharmaceutical Co. Ltd., Japan). Assays were performed within three hours after blood collection. The cross-reactivity of estrone with the estradiol kit was less than 0.7%.

**Herbal Preparation**

Dang-gui-shao-yao-san (Toki-shakuyaku-san) and Gui-zhi-fu-ling-wan (Keishi-bukuryo-gan) are composed of six and five herbal drugs, respectively, and Wen-jing-tang is composed of 11 herbal drugs and one preparation derived from animal materials (aqueous gelatin) (Table 2).

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<tr>
<th>The Eight-Principle Pattern Identification</th>
<th>Abdominal Findings</th>
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<td><strong>Dang-gui-shao-yao-san</strong></td>
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<td>Hypofunctioning condition (xu zheng)</td>
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<td>Cold syndrome (han zheng)</td>
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<td>Blood deficiency (xue xu)</td>
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<td>Disorders of the body’s fluid metabolism (shui du)</td>
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<td>Hyperfunctioning condition (shi zheng)</td>
<td>Resistance and tenderness on</td>
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<td>Heat syndrome (re zheng)</td>
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<td>Blood stagnation (yu xue)</td>
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<td>Hypofunctioning condition (xu zheng)</td>
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<td>Blood deficiency (xue xu)</td>
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<td>Blood stagnation (yu xue)</td>
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<td>Qi deficiency (qi xu)</td>
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Dang-gui-shao-yao-san is a combination of six herbal drugs: 4 g each of Peony root (shao yao), Atractylodes Lancea rhizome (cang shu), Alisma rhizome (ze xie), and Hoelen (fu ling); and 3 g each of Cnidium rhizome (chuan xiong) and Japanese Angelica root (dang gui). A mixture consisting of these chopped ingredients was extracted with 1 liter of hot water, condensed by boiling to 600 ml and filtered and lyophilized to prepare lyophilized powder which was stored at 4°C as 4 g of Dang-gui-shao-yao-san 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).

Gui-zhi-fu-ling-wan is a combination of 5 herbal drugs: 3 g each of Cinnamon bark (gui pi), Peony root (shao yao), Peach kernel (tao ren), Hoelen (fu ling), and Moutan bark (mu dan pi). Lyophilized powder, produced by the same process as described above, was processed to obtain granules for commercial preparation (7.5 g of granular-type agent containing 2.5 g of drug additive, i.e. lactose) (Tsumura & Co., Tokyo, Japan).

Wen-jing-tang (Unkei-to) is a combination of 11 herbal drugs and one preparation derived from animal material (Asini Corii Collas, aqueous gelatin; e jiao). This herbal powdered ingredient consists of 4 g each of Ophiopogon tuber (mai men dong) and Pinelliae tuber (ban xia); 3 g of Japanese Angelica root (dang gui); 2 g each of Glycyrrhiza root (gan cao), Cinnamon bark (gui pi), Peony root (shao yao), Cnidium rhizome (chuan xiong), Ginseng radix (ren shen), and Moutan bark (mu dan pi); and 1 g each of Evodia fruit (wu zhu yu) and Ginger rhizome (sheng jiang). Lyophilized powder, produced by the same process as described above, was processed to obtain granules for commercial preparation (7.5 g of granular-type agent containing 2.5 g of drug additives, i.e. lactose) (Tsumura & Co., Tokyo, Japan).
Statistical Analysis

Results are expressed as mean ± SD. Statistical analysis was performed using the Wilcoxon signed-rank test for inter- and intra-group comparisons, and the chi-square test to compare proportions. p < 0.05 values were considered significant.

Results

The percentage of women with successful ovulation was 15.6% (10/64) after the 8-week administration of an appropriate Kampo prescription selected based on SHO and Kampo diagnosis (Dang-gui-shao-yao-san: 16.3%, Gui-zhi-fu-ling-wan: 4.8%). There was no significant difference between the baseline plasma FSH and LH levels (5.11 ± 1.31 mIU/ml and 14.9 ± 3.25 mIU/ml) and the levels after 8 weeks of treatment with Dang-gui-shao-yao-san (4.43 ± 1.11 mIU/ml and 14.5 ± 3.88 mIU/ml). In treatment with Gui-zhi-fu-ling-wan, plasma levels of FSH and LH were also unchanged after 8 weeks (4.91 ± 0.70 mIU/ml and 14.9 ± 3.25 mIU/ml) compared with baseline levels (4.85 ± 0.98 mIU/ml and 15.02 ± 3.45 mIU/ml). Plasma levels of estradiol were also unchanged after 8 weeks (41.3 ± 3.5 pg/ml and 56.7 ± 12.2 mIU/ml) compared with baseline levels (41.3 ± 3.5 pg/ml and 56.7 ± 12.2 mIU/ml) with treatment with Dang-gui-shao-yao-san and Gui-zhi-fu-ling-wan, respectively. The limits of detection of the assays were 1 mIU/ml, 1 mIU/ml, and 20 pg/ml, and intra-assay CVs were 2.01%, 2.59%, and 2.79% for FSH, LH, and estradiol, respectively.

Fifty-four patients did not achieve successful ovulation after the 8-week administration of Dang-gui-shao-yao-san (38 cases) or Gui-zhi-fu-ling-wan (16 cases). They were randomly allocated to either of two treatment groups as described above. Comparison between the patients who continued the preceding Kampo prescription and those who switched to Wen-jing-tang revealed no differences in age, BMI, duration of amenorrhea, or plasma endocrine levels (Table 3).

In both the groups switching from Dang-gui-shao-yao-san (−58.2%, p < 0.0001) and that switching from Gui-zhi-fu-ling-wan (−49.4%, p = 0.0005), plasma levels of LH decreased significantly compared with those at the start of Wen-jing-tang administration (Fig. 1). Furthermore, there were significant differences in the extent

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<th>Table 3. General Characteristics of the Study Population</th>
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<td>Age (years)</td>
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<td>BMI (kg/m²)</td>
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<td>Months of Amenorrhea</td>
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<td>FSH (mIU/ml)</td>
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of reduction of plasma LH levels between the switching group and continuation group (Dang-gui-shao-yao-san = 10.9%, p < 0.0001, Gui-zhi-fu-ling-wan = 8.6%, p = 0.0005).

In the group switched from Dang-gui-shao-yao-san, a tendency towards increase in plasma estradiol level was observed (1.51-fold, p = 0.055), which was significant compared with that in the group switched from Gui-zhi-fu-ling-wan (decreased 16.7%, p = 0.032).

In the switching groups, the rate of achievement of ovulation increased significantly after the 8-week administration of Wen-jing-tang (59.3%, 16/27) compared with that after treatment with the preceding Kampo prescription (7.4%, 2/27). A significantly (p = 0.0036) higher percentage of women with successful ovulation was observed in the group.
switching to Wen-jing-tang from the preceding Kampo prescription (overall achievement rate = 59.3%) than in the continuation group (7.4%, Table 4).

On the other hand, a significant difference in rate of successful ovulation was observed between the group switching from Dang-gui-shao-yao-san (68.4%, 13/19) and that switching from Gui-zhi-fu-ling-wan (37.5%, 3/8, p = 0.429). After the 16-week continuous treatment with Kampo prescriptions, the rates of achievement of ovulation were 18.6% (8/43) and 19.0% (4/21) in the groups treated with Dang-gui-shao-yao-san and Gui-zhi-fu-ling-wan, respectively.

Discussion

Polycystic ovary syndrome is characterized by onset at a relatively young age among the various disturbances of ovulation, and Japanese women affected by it tend to be lean with normal testosterone level. Clomiphene treatment and gonadotropin therapy (with pure FSH) have conventionally been used for the treatment, though they have not been sufficiently successful in stimulating ovulation (Singh et al., 1992; Berg et al., 1994; Murakawa et al., 1999). In PCOS or ovulatory failure with high plasma LH levels, Wen-jing-tang has been shown to decrease plasma LH levels and dramatically increases clinical ovulation rate (Ushiroyama et al., 2001; Ushiroyama, 2003), though the mechanism by which is still unclear.

Prescriptions of Kampo preparations are determined by using traditional diagnostic procedures, the eight-principle pattern identification, the diagnostic process, and logic based on the state of the qi, blood and water or the five parenchymatous viscera (Ushiroyama, 2005; Wiseman and Ellis, 1996). Thus, therapeutic effect depends on the appropriateness of matching of the selected Kampo preparation with the constitution and resistance to disease of individual patients, as well as the disease stage, meaning that appropriate prescription cannot be determined based on the diagnosis of a disease alone (Ushiroyama, 2004 and 2005). However, it has been demonstrated in previous clinical studies that Wen-jing-tang has definite endocrinological effects apart from strict application of traditional diagnostic procedures of oriental medicine and theories of herbal medicine (Ushiroyama et al., 2001, 2002, 2003a and b; Ushiroyama, 2003). Moreover, a study in which patients with disturbance of ovulation were divided into groups with excess and deficiency based on individual eight-principle patterns found no significant difference between groups in the effect of Unkei-to in terms of endocrinological responsiveness (Ushiroyama et al., 2003b).
In the present study, Kampo prescription was first selected based on the eight-principle pattern identification, the diagnostic process and logic based on the state of qi, blood and fluids, and the traditional Kampo diagnostic procedure. In the patients who had not achieved successful ovulation after the 8-week administration of an appropriate Kampo prescription, we compared the changes in endocrine levels and rates of achievement of ovulation between switching treatment to Wen-jing-tang and continuation of treatment with the preceding Kampo prescription. Switching of treatment to Wen-jing-tang for 8 weeks from either Kampo prescription, the plasma LH levels were significantly decreased. Switching also resulted in a six-fold higher ovulation rate than that after continuation of treatment with the preceding Kampo prescription. These results may be interpreted as follows:

(1) The initial 8-week treatment with Kampo prescription in accordance with eight-principle pattern identification and Oriental medical pathology restored and regulated “distortion” of the body, yielding a situation in which an abnormal endocrinological condition was likely to respond to Wen-jing-tang.

(2) Since the results of switching treatment in this study did not differ from those for ovulation after treatment with Wen-jing-tang as the initially chosen drug (Ushiroyama et al., 2001; Ushiroyama, 2003), it seems that the pathology of PCOS cannot be determined by the eight-principle pattern identification or Oriental medical findings (no physical findings of current PCOS are described in any classical articles on herbal medicine). PCOS can only be clarified with the use of modern scientific techniques, and only Wen-jing-tang has a therapeutic effect against this disease.

Among many Kampo preparations, Wen-jing-tang is the one for which the largest amount of data is available to determine a mechanism of action with scientific methodology. In herbal medicine, therapeutic drugs selected based on the diagnosis of eight-principle pattern identification specific to individual patients are considered likely to be effective. This study confirmed that Wen-jing-tang improves endocrine condition without taking into consideration eight-principle pattern identification and Kampo diagnosis based on the concept of pathological condition of qi, blood, and fluids, and suggested that it may become a potent therapeutic agent in future clinical practice.

References


