A Four Step Protocol for Improving the Effects of Clomiphene in Patients with Ovulatory Dysfunction

abstracted & translated by
Bob Flaws, L.Ac., FNAAOM (USA), FRCHM (UK)

On page 405 of issue #7, 2007 of the Zhe Jiang Zhong Yi Za Zhi (Zhejiang Journal of Chinese Medicine), Shi Jian-jun et al. published an article titled “Clinical Observations on A Four Step Method for Regulating Menstruation on Improving the Adverse Effects After Clomiphene Induction of Ovulation.” A summary of this article is presented below.

Cohort description: A total of 110 patients diagnosed with female infertility were enrolled in this two-wing comparison study. These 110 were then randomly divided into two groups – a treatment group of 60 and a comparison group of 50. Within the treatment group, the median age in these patients was 29.17 ± 3.50 years, and the median duration of infertility was 4.23 ± 1.81 years. Forty-four cases suffered from primary onset infertility and 16 cases from secondary infertility. In the comparison group, the median age was 29.60 ± 3.23 years, and the median duration of infertility was 4.10 ± 1.75 years. Thirty-eight of these cases suffered from primary onset infertility and 12 cases from secondary onset infertility. Therefore, for the purposes of this study, these two groups were deemed statistically comparable in terms of age, disease duration, and type of infertility.

Treatment method: All members of the treatment group received the following four step protocol for the regulation of menstruation with Chinese medicinals.

Menstrual period: In order to warm the menses and scatter cold, quicken the blood and transform stasis, Shao Fu Zhu Yu Tang (Lesser Abdomen Dispel Stasis Decoction) with additions and subtractions was administered:
Dang Gui (Radix Angelicae Sinensis)
uncooked Pu Huang (Pollen Typhae)
stir-fried Wu Ling Zhi (Feces Trogopterori)
Yan Hu Suo (Rhizoma Corydalis), 10g each
Chi Shao (Radix Rubra Paeoniae)
Chuan Xiong (Rhizoma Chuanxiong)
Gan Cao (Radix Glycyrrhizae), 9g each
Xiao Hui Xiang (Fruit Foeniculi), 12g
stir-fried Ru Xiang (Olibanum)
stir-fried Mo Yao (Myrrha), 6g each
Rou Gui (Cortex Cinnamomi), 5g

Post-menstrual period: In order to increase essence and boost the kidneys, nourish the blood and regulate menstruation, Yi Shen Tiao Xue Tang (Boost the Kidneys & Regulate Menstruation Decoction) with additions and subtractions was administered:
Shu Di (cooked Radix Rehmanniæae)
Shan Zhu Yu (Fructus Corni)
Nu Zhen Zi (Fructus Ligustri Lucidi)
Tu Si Zi (Semen Cuscutae)
Rou Cong Rong (Herba Cistanchis), 12g each
Dang Gui (Radix Angelicae Sinensis)
stir-fried Shan Yao (Radix Dioscoreæae)
stir-fried Xiang Fu (Rhizoma Cyperi)
Gan Cao (Radix Glycyrrhizae), 10g each

Midcycle: In order to boost the kidneys and course the liver, quicken the blood and free the flow of the network vessels, Shu Gan Huo Xue Tang (Soothe the Liver & Quicken the Blood Decoction) with additions and subtractions was administered:
Bai Shao (Radix Alba Paeoniae)
Mai Ya (Fructus Germinatus Hordei)
Shi Xian Chuan (Squama Manitis)
Lu Jiao Pian (Cornu Cervi), 12g each
Dang Gui (Radix Angelicae Sinensis)
Dan Shen (Radix Salviae Miltiorrhizæae), 10g each
Chai Hu (Radix Bupleuri)
Gui Zhi (Ramulus Cinnamomii)
Gan Cao (Radix Glycyrrhizae), 9g each
Shui Zhi (Hirudo), 6g

Premenstruum: In order to warm yang and boost the kidneys, Wen Yang Yi Shen Tang (Warm Yang & Boost the Kidneys Decoction) with additions and subtractions was administered:
Tu Si Zi (Semen Cuscutae)  
Zi Shi Ying (Flouritum)  
Xian Ling Pi (Herba Epimedii)  
She Chuang Zi (Semen Cnidii)  
Shu Di (cooked Radix Rehmanniae)  
Sang Ji Sheng (Herba Taxilli), 12g each  
Xiang Fu (Rhizoma Cyperi)  
Gan Cao (Radix Glycyrrhizae), 9g each  
Dang Gui (Radix Angelicae Sinensis), 10g  
Ba Ji Tan (Radix Morindae Officinalis), 15g

When it says “with additions and subtractions” above, it means that these base formulas were modified according to each patients presenting patterns. Both groups also were administered 50-100 milligrams of clomiphene per day beginning on day five and continuing for five days. One month equaled one course of treatment, and results were analyzed after three such courses.

Study outcomes: In the treatment group, there were a total of 152 menstrual cycle with 127 ovulations (83.6%). In addition, there was a conception rate of 41.7%. In the comparison group, there were 137 menstrual cycles with 102 ovulations (74.5%) and only a 22% conception rate. Thus there was no marked difference in the total ovulatory rate between these two groups but there was a significant difference in the rate of conception. In addition, Insler scores were tabulated for all members of both groups before and after treatment. The Insler score is a way of scoring the quality of vaginal mucus at ovulation. A score (out of 12) for the quality of cervical mucus, gauged by scoring each of the following from 0 to 3: 1) The cervix should be open and the volume of mucus should be good. Although every woman will be different for both these parameters, they will be consistent in one woman from ovulation to ovulation. 2) The mucus should be clear, watery, and stretchy (Spinnbarkkeit). And 3) the mucus should produce a complete “ferning” pattern when it is allowed to dry on a microscope slide. The first two criteria vary at ovulation in different women (so anything above a score of 9 or 10 can be normal), but the same woman should achieve the same cervical score from one ovulation to the next. The following table shows the median Insler scores for the two groups. This chart also shows the mean thickness of the endometrium in both groups before and after treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Insler score</th>
<th>Endometrial thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Before treatment</td>
<td>3.37 ± 2.06</td>
<td>0.62 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>8.14 ± 2.12</td>
<td>0.85 ± 0.17</td>
</tr>
<tr>
<td>Comparison</td>
<td>Before treatment</td>
<td>3.28 ± 2.00</td>
<td>0.63 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>6.53 ± 2.64</td>
<td>0.69 ± 0.24</td>
</tr>
</tbody>
</table>

As this table shows, the mean Insler score in the group which received both the Chinese medicinals and clomiphene was much higher after treatment than that of the group which only received the clomiphene. In addition, there was also a significantly thicker endometrium in the treatment group after treatment than in the comparison group. And finally, after treatment, the menstrual cycle was normal in 47 patients (78.3%) in the treatment group compared to only 30 cases (60%) in the comparison group.

Discussion: According to the authors of this study, ovulatory dysfunction is a main cause of female infertility, and clomiphene citrate is commonly used to induce ovulation in such women. However, the conception rate with this drug does not correspond to what one would like. Unfortunately, using the four step method of regulating menstruation does not achieve as high a rate of ovulation as does clomiphene. Therefore, the authors of this study decided to combined the use of clomiphene with this four step menstruation-regulating method. During menstruation, the sea of blood is full and exuberant and is the time for its discharge. During that time, the use of blood-quickening and stasis-transforming medicinals benefits corpus luteum by promoting the complete shedding of the endometrial lining. After menstruation, the blood is consumed and damaged and the sea of blood is empty and vacuous. Now, medicinals for increasing the essence and boosting the kidneys not only increases serum estrogen levels but also improves the cervical mucus, thus making it easier for the sperm to penetrate it. It also promotes the growth of the endometrial lining. Midcycle, yin transform into yang. Therefore, boosting the kidneys and coursing the liver, quickening the blood and freeing the flow of the network vessels can promote the maturation and the expulsion of the ovum. It also insures a healthy environment for the zygote to implant in the endometrium. During the premenstruum, kidney yang qi gradually becomes effulgent, and eventually, double yang transforms into yin. At this time the use of medicinals to warm and supplement kidney yang along with kidney yin supplementing medicinals, further promotes the proper environment for the zygote to implant and develop. Not only does the combination of clomiphene with this four step method improve the conception rate, it also has no adverse side effects. Therefore, the authors believe this method achieves relatively good therapeutic effects.