

Ovarian Hyperstimulation Syndrome and Chinese Medicine

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Western drugs used to stimulate the ovaries in the treatment of infertility might cause side effects. These side effects can range from mild to severe and, in rare cases, may even be life-threatening. Excessive stimulation of the ovaries is called ovarian hyperstimulation syndrome (OHSS). Resulting high levels of estrogen (E2) and progesterone (P) in the bloodstream might upset the digestive system and fluid balance, causing abdominal bloating and tenderness, nausea, diarrhea and weight gain. If the condition is more severe, there also might be vomiting, scanty dark urine, dry skin and hair, and thirst. If the symptoms are even more severe, there might be shortness of breath, anuria and calf and/or chest pain.

If the woman's menses starts, she is likely to begin feeling better. However, pregnancy may prolong or exaggerate these side effects, and it might take up to 10 weeks for the symptoms to resolve during pregnancy. In severe cases, the patient might need to be assessed at the hospital or at a fertility clinic, and excess fluid will need to be removed from the abdominal cavity via abdominal paracentesis.¹ Complications associated with severe OHSS include blood-clotting disorders, kidney damage and twisted ovary (ovarian torsion).²

Incidence

Ovarian hyperstimulation syndrome is the most serious complication of *in vitro* fertilization (IVF). Any patient undergoing artificial induction of ovulation is at risk of developing OHSS, although some are more at risk than others. The symptoms usually begin four to five days after the egg collection. Up to 33 percent of IVF treatments have been reported to be associated with mild forms of OHSS, while severe OHSS has been reported in 3-8 percent of IVF cycles. Women who are at risk of developing OHSS include:

1. Those with polycystic ovaries. There is evidence that adding metformin to ovulation induction in women with polycystic ovarian syndrome (PCOS) undergoing IVF treatment reduces the risk of developing OHSS.
2. Younger women.
3. Women with high estrogen hormone levels and a large number of follicles or eggs.
4. Administration of gonadotropin-releasing hormone (GnRh) agonist.
5. The use of human chorionic gonadotropin (hCG) for luteal-phase support.³

Etiology

Clomifene citrate therapy can occasionally lead to OHSS, but the vast majority of cases develop after use of gonadotropin therapy such as Pergonal (with administration of follicle-stimulating hormone or FSH), and administration of hCG to trigger ovulation, often in conjunction with IVF.⁴

Pathophysiology

OHSS is characterized by the presence of multiple luteinized cysts within the ovaries, leading to ovarian enlargement and secondary complications. As the ovary undergoes a process of extensive luteinization, large amounts of estrogens, progesterone and local cytokines are released. It is believed that vascular endothelial growth factor (VEGF) is a key substance that induces OHSS by making local capillaries "leaky," leading to a shift of fluids from the intravascular system to the abdominal and pleural cavities. Thus, while the patient accumulates fluid in the third space, primarily in the form of ascites, she actually becomes hypovolemic and is at risk for respiratory, circulatory and renal problems. Patients who are pregnant sustain this ovarian luteinization process by the endogenous production of hCG.⁵

Chinese Medicine and OHSS

The first Chinese article I have seen on this condition was a 2007 *Journal of Chinese Medicine* article, "The Effects of *Yi Shen Li Shui Fang* (Boosting the Kidneys and Disinhibiting Water Formula) on the Vascular Permeability of Patients with Ovarian Hyperstimulation Syndrome."⁶ It is a report on a two-wing, randomized clinical trial comparing treatment between integrated Chinese-Western medicine and Western medicine alone. It is summarized in English below.

Cohort Descriptions

Thirty women diagnosed with OHSS were randomized into two groups of 15 cases each, a treatment group treated with integrated Chinese-Western medicine and a comparison group treated with only Western medicine. In the treatment group, the women were 26 to 38 years old, with a median age of 31.67 ± 3.75 years. In five cases, the cause of infertility was fallopian tube dysfunction, while there were four cases of ovulatory dysfunction, three cases of immune infertility, two cases of male sterility and one case of infertility of unknown etiology. Nine of these cases suffered from moderate OHSS, and six cases suffered from severe OHSS. Ovulation was stimulated with a combination of gonadotropin-releasing hormone agonist (GnRH-a) and gonadotrophins (GN).

In the comparison group, the age range was from 22 to 35 years, with a median age of 29.73 ± 3.85 years. In this group, there were six cases of fallopian tube dysfunction, four cases of male sterility, three cases of ovulatory dysfunction, one case of immune infertility and one case of infertility of unknown etiology. Ten of these women suffered from moderate OHSS and the other five suffered from severe OHSS. Stimulation of ovulation was the same as for the treatment group.

In addition, there were another 15 women who had undergone IVF but did not have OHSS. These women were 19 to 37 years old, with a mean age of 30.71 ± 3.92 years. Five of these women had fallopian tube dysfunction and three had ovulatory dysfunction. There also were three cases of male sterility, two cases of immune infertility and two cases of infertility of unknown etiology. These women's ovulation also was stimulated by the same method described previously. The women in this group served as a normal control.

Treatment Methods

Both groups that exhibited the symptoms of OHSS received the same standard Western medical care. This consisted of numerous tests and examinations to monitor their condition, diet and lifestyle modifications, intravenous hydration with 500-100 mL of glucose solution, and possible intramuscular injection of 50 mg of progesterone per day for 10 days. As the patients' symptoms of OHSS decreased, their treatment was gradually reduced or stopped. Typically, symptoms did not last more than three months. Members of the treatment group were also administered a basic Chinese medicinal formula consisting of:

shu di huang (cooked *Radix rehmanniae*)
shan zhu yu (*Fructus corni*)
 15 g *shan yao* (*Radix dioscoreae*)
fu ling (*Poria*)
 10 g each *ze xie* (*Rhizoma alismatis*)
 30 g *huang qi* (*Radix astragali*)
yin yang huo (*Herba epimedii*)
tu si zi (*Semen cuscutae*)
ren shen (*Radix ginseng*)
bai zhu (*Rhizoma Atractylodis macrocephalae*)
 12 g *dan shen* (*Radix salviae miltiorrhizae*)

If edema was marked, 20 grams of *zhu ling* (*Polyporus*) was added to the above formula and the amounts of *fu ling* and *ze xie* were increased. If there was marked ovarian enlargement or blood-quickening, stasis-transforming medicinals were added, such as 10 grams of *dang gui* (*Radix angelicae sinensis*). If the woman was pregnant, *bai zhu* was increased to 15 grams and 15 grams of *xu duan* (*Radix dipsaci*) were added to boost the *qi* and quiet the fetus. If there was nausea and vomiting, three slices of *sheng jiang* (uncooked *Rhizoma zingiberis*) and 10 grams of ginger-processed *ban xia* (*Rhizoma pinelliae*) were added to downbear the counterflow and stop vomiting.

One packet of these medicinals was decocted in water down to 300 ml of medicinal fluid and administered in two divided doses per day. However, if there was nausea and vomiting, small amounts of this liquid were administered in numerous doses throughout the day. Five packets equaled one course of treatment, and two continuous courses were typically administered. Outcomes were analyzed after 10 days of continuous treatment in both groups. In a few cases where there was mediocre improvement or no effect, treatment was continued longer until the patient was either cured or improved.

Study Outcomes

Cure was defined as basic disappearance of nausea, abdominal distention, ascites and water in the chest. In addition, abdominal circumference and body weight gradually returned to normal and the ovaries on both sides were less than 3 centimeters large. Improvement was defined as remission of such symptoms as nausea, abdominal distention, ascites and water in the chest. Abdominal circumference had shrunk and body weight has lessened, however, they had not yet returned to normal. Further, the size of the ovaries had not increased. No effect meant that, after three courses of treatment, there was no reduction in the above signs and symptoms or the condition had gotten progressively worse. The following table presents these outcomes in the two groups that underwent treatment.

Group	Cured	Improved	No effect	Total effect
Treatment	10 (66.67%)	5 (33.33%)	0	15 (100%)
Comparison	4 (40.00%)	10 (53.33%)	1 (6.67%)	14 (93.33%)

This shows that, though the total effectiveness rate was comparable, significantly more members of the treatment group were cured by the integrated Chinese-Western medicine protocol. The next table shows the comparative rates of the necessary use of albumin administration and large-volume paracentesis (LVP).

Group	Albumin	LVP
Treatment	6 (40.00%)	3 (20.00%)
Comparison	12 (80.00%)	9 (60.00%)

Only half the number of women had to use albumin in the treatment group as opposed to the comparison group, while the necessary use of LVP in the treatment group was only one-third that in the comparison group. In addition, the patients in the treatment group only spent an average of 11.2 days each in the hospital, as opposed to 14.4 days in the comparison group.

Finally, the mean vascular endothelial growth factor (VEGF) in the treated group decreased to normal range, as compared to the non-OHSS group, while the mean VEGF in the comparison group remained notably higher than in the healthy control group.⁷ There is evidence the major capillary permeability agent in OHSS ascites fluid is VEGF.⁸

Therefore, the authors of this study concluded that treating OHSS with integrated Chinese-Western medicine is more effective than standard Western medical treatment alone. In addition, they believe the research shows this integrated Chinese-Western medical treatment does address one of, if not the main, mechanisms of vascular permeability in OHSS.

Discussion

According to the Chinese authors of this study, the presenting symptoms of water in the chest, ascites, generalized edema and ovarian hypertrophy correspond to the traditional Chinese medical disease categories of child or fetal swelling (*zi zhong*, i.e., edema during pregnancy), water swelling (*shui zhong*), drum distention (*gu zhang*), and accumulations and gatherings (*ji ju*). They further believe the main Chinese medical disease mechanism of this disorder is kidney vacuity, resulting in water rheum collecting and stagnating that can then "reach" or affect the spleen and heart viscera. It also is possible for *qi* stagnation and blood stasis to result in the production of accumulations and gatherings. According to Chinese medical theory, "The kidneys govern water fluids and command *qi* transformation." In other words, the *qi* transformation function of kidney *yang* is closely tied to the water metabolism of the human body. Therefore, in this case, water fluid metabolism is abnormal and there arises ascites, water in the chest and generalized edema.

Based on this scenario, the authors believe kidney vacuity is the root of this condition, while water rheum collecting and stagnating, mixed with *qi* stagnation and blood stasis, are the tips or branches of the condition. Therefore, in order to remedy this situation, they posit that one should supplement the kidneys and foster essence, warm *yang* and disinhibit water. This addresses the root mechanism of this condition. Then, depending on the differing symptoms of various individuals, one also might need to quicken the blood and transform stasis, boost the *qi* and fortify the spleen, etc.

Hence, within the previously mentioned formula, *shu di huang*, *shan zhu yu*, *shan sao*, *yin yang huo* and *tu si zi* supplement the kidneys and invigorate *yang*. *Ren shen*, *huang qi* and *bai zhu* fortify the spleen and boost the *qi*. *Fu ling* and *ze xie* disinhibit water and free the flow of urination, and *dan shen* quickens the blood and transforms stasis. Taken as a whole, this formula's effects are to boost the kidneys, warm *yang* and disinhibit water. This formula can be further modified with additions and subtractions, based on each patient's personally presenting signs and symptoms and disease condition.

References

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3. *Ibid.*

4. Ovarian Hyperstimulation Syndrome. http://en.wikipedia.org/wiki/Ovarian_hyperstimulation_syndrome.
5. *Ibid*.
6. Liu FY, et al. The effects of *yi shen li shui fang* (boosting the kidneys and disinhibiting water formula) on the vascular permeability of patients with ovarian hyperstimulation syndrome. *Zhong Yi Za Zhi (Journal of Chinese Medicine)*, 2007;11:989-91.
7. Vascular endothelial growth factor (VEGF) is a subfamily of growth factors, more specifically of the platelet-derived growth-factor family of cystine-knot growth factors. They are important signaling proteins involved in both vasculogenesis (the *de novo* formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature). Vascular endothelial growth factor is a polypeptide structurally related to platelet-derived growth factor (PDGF).
8. McClure N, Healy DL, Rogers PA, et al . Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. *Lancet*, 1994 Jul 23;344(8917):235-6.

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