OVARIAN HYPERSTIMULATION SYNDROME: A CURRENT SURVEY

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Increased understanding of the physiology of ovulation has given rise to progress in the therapeutic induction of ovulation. This has been accomplished following the early experiments of Cushing, who showed the dependence of gonadal function on the pituitary, and the findings of Zondek, who demonstrated the biologic properties of individual gonadotropins in experimental animals.

Toward the end of the 1930s, equine serum gonadotropin extracted from pregnant mare serum (PMSG) was applied in clinical trials to stimulate the ovaries in order to induce ovulation, resulting in corpus luteum formation and pregnancy.1 The results, however, were inconsistent and generally disappointing owing to the formation of neutralizing antibodies to heterologous gonadotropin.

In 1958, Gemzell et al.2 first described the successful induction of ovulation and pregnancy in humans, utilizing follicle-stimulating hormone (FSH) derived from human pituitary glands (HPG) removed at autopsy, in combination with human chorionic gonadotropin (HCG). In 1961 Greenblatt and Barfield3 introduced clomiphene citrate as a successful agent for ovulation induction. Subsequently, Lunenfeld4 was the first to use gonadotropin derived from human menopausal urine (HMG) for the induction of ovulation.

With the use of these agents, a series of complications has been described in the literature, coming under the general term of ovarian hyperstimulation syndrome (OHSS). The seriousness of this iatrogenic syndrome is reflected in the fact that deaths have been reported resulting from this treatment.5-8

During the last 12 years we have had experience with 25 patients hospitalized with OHSS. Our aim here is to discuss the clinical and laboratory findings in OHSS, to outline the pathogenesis, and to present a plan for prevention and management.

INCIDENCE

The incidence of OHSS varies with the different clinical conditions in which ovulation is induced, the types of preparations administered, and the doses and schedules administered.

PMSG. Until 1961, 60 cases of hyperstimulation, including two deaths, were reported in patients treated with PMSG.7, 8

HMG. Several cases of OHSS due to the administration of HMG have been reported in detail, including deaths due to thromboembolic phenomena.5, 6, 9-12 Reports of the incidence of OHSS due to HMG-HCG treatment are summarized in Table 1.

Ovarian hyperstimulation is more frequent in patients who have conceived after induction of ovulation. Hack et al.22 reported a 6% incidence of severe OHSS in such patients. Some type of OHSS was observed in 50% of patients during the cycle in which conception resulted from ovulation induction.17 With present methods of monitoring gonadotropin therapy, the incidence of OHSS is lower than that summarized in Table 1. Even when estrogen levels were monitored, however, Taymor et al.23 did not reduce the incidence of mild hyperstimulation (12% to 15%), but the severe cases were prevented.

HPG. The incidence of hyperstimulation using gonadotropin extracted from human pituitary has varied greatly from one group to another.24-27 In 1963 Gemzell24 reported that this syndrome had occurred 4 times in 22 treatment cycles, but in 1970, by monitoring estrogen levels during
TABLE 1. Incidence of OHSS Due to HMG-HCG Treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<td></td>
<td>No. of patients</td>
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<tr>
<td>Vande Wiele and Turksoy</td>
<td>35</td>
<td>3</td>
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<td>119</td>
<td>8.4</td>
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<tr>
<td>Lunenfeld and Insler</td>
<td>1405</td>
<td>119</td>
<td>8.4</td>
<td>20</td>
<td>6</td>
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<tr>
<td>Thompson and Hansen</td>
<td>3002</td>
<td>119</td>
<td>8.4</td>
<td>12</td>
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<tr>
<td>Caspi et al.</td>
<td>101</td>
<td>343</td>
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<td>40</td>
<td>1.2</td>
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<tr>
<td>Tyler</td>
<td>236</td>
<td>109</td>
<td>23</td>
<td>7</td>
<td>1.5</td>
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<tr>
<td>Goldfarb and</td>
<td>292</td>
<td>67</td>
<td>10</td>
<td>15</td>
<td>1.8</td>
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<tr>
<td>Rakoff</td>
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<td>3</td>
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<td>Jewelewicz et al.</td>
<td>101</td>
<td>42</td>
<td>20</td>
<td>4</td>
<td>1.8</td>
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<tr>
<td>Hammond and</td>
<td>30</td>
<td>6</td>
<td>21</td>
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<tr>
<td>Marshall</td>
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<tr>
<td>Taymor</td>
<td>55</td>
<td>11</td>
<td>20</td>
<td>4</td>
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courses of treatment, only 1 case of hyperstimulation was observed; the same preparation was used for all patients.

Clomiphene Citrate. The incidence of mild OHSS with clomiphene therapy for induction of ovulation has been reported in 13.5% of 8029 patients. Severe OHSS with clomiphene treatment is rare, but has been reported. Southan and Janovsky studied a patient with Stein-Leventhal syndrome who developed massive ovarian enlargement, ascites, and hydrothorax after the administration of 100 mg of clomiphene citrate for 14 days. A case of severe ovarian hyperstimulation associated with conception, similar to that observed in one of our patients, was reported by Scommegna and Lash. Combined therapy with clomiphene and HMG may also result in OHSS.

CLINICAL SYMPTOMS AND SIGNS

Various clinical aspects of severe OHSS have been described in detail after treatment with HMG-HCG, HPG-HCG, and clomiphene citrate. Based on the severity of the symptoms, signs, and laboratory findings, the accepted qualification in the literature is that of Rabau et al., who classified ovarian response into three main clinical categories and six grades.

Categories

Mild Hyperstimulation

Grade 1. This grading consists only of laboratory findings of hyperstimulation: estrogen levels above 150 μg/24 hours and pregnanediol excretion above 10 mg/24 hours.

Grade 2. The above laboratory findings are present plus enlargement of ovaries; sometimes small cysts are palpable.

Moderate Hyperstimulation

Grade 3. In addition to elevated urinary steroid levels and ovarian cysts, abdominal distention is present.

Grade 4. This grading consists of criteria of grade 3, plus vomiting and/or diarrhea.

Severe Hyperstimulation

Grade 5. In addition to the above, the ovarian cysts are large and ascites and/or hydrothorax are present.

Grade 6. Marked hemoconcentration with increased blood viscosity may result in coagulation abnormalities.

Grades

Grade 1. Chemical hyperstimulation is a very common accompaniment of ovulation induction. It is of little clinical concern, and usually resolves with the onset of menses. Chemical hyperstimulation may follow HCG administration or even occur with HPG or HMG alone.

Grade 2. The mild form of this syndrome presents as a feeling of abdominal heaviness, tension, swelling, and pain. The physical findings are bilateral ovarian enlargement by multiple follicular and corpus luteum cysts, measuring up to 5 x 5 cm. In recent years, this category has been relatively much more common than severe OHSS, owing to estrogen monitoring. The symptoms and physical findings of enlarged ovaries usually begin 3 to 6 days after HCG administration. Ovarian hyperstimulation is encountered only if the patient has ovulated. Therefore, it will not develop if the ovulatory dose of HCG is withheld. Nevertheless, sporadic cases have been observed following HPG or HMG alone. If pregnancy does not occur, the ovarian enlargement gradually declines until menses, after which time the decline
accelerates. If conception occurs, further ovarian enlargement generally follows late in the cycle because of additional endogenous HCG stimulation, and this may present during the first trimester of pregnancy. In the mild form of the syndrome, no therapy is necessary except for rest, observation, and medication for symptomatic relief. Occasionally the cyst may rupture or undergo torsion and thus present as an acute abdomen.

**Grades 3 and 4.** In cases of moderate hyperstimulation, the abdominal discomfort is more pronounced. Gastrointestinal symptoms such as nausea, vomiting, and (less frequently) diarrhea are present. There is some gain in weight, and the ovaries are enlarged (up to 12 × 12 cm). Symptoms of moderate severity usually subside spontaneously with rest in bed for 2 or 3 weeks. Patients in this category require close observation since they may progress rapidly to the severe form, especially if conception occurs. It is thus of importance to confirm conception as early as possible by serial estimation of β-HCG levels in the blood. The possibility of rupture of an ovarian cyst should always be considered. Pelvic examination, therefore, must be gentle so as to minimize the likelihood of rupture which may result in intraperitoneal hemorrhage.

**Grades 5 and 6.** Severe OHSS is a serious complication of therapy given to a previously healthy woman. The clinical manifestations include ascites, pleural effusion, electrolyte imbalance, hypovolemia, oliguria, and even hypovolemic shock. The ovaries are greatly enlarged (more than 12 cm in diameter) and are easily palpable abdominally. An exceptional case of severe OHSS with acute pleural effusion, but without ovarian enlargement, has been reported.

In extreme cases there is severe hemoconcentration, increased blood viscosity, and thromboembolic phenomena. The clinical symptoms and signs in patients hospitalized in our department are summarized in Table 2. In most cases, symptoms and signs appeared 3 to 10 days after the administration of HCG. In 10 patients, hyperstimulation was associated with conception.

The obstetric results in those cases of hyperstimulation associated with pregnancy were two quintuplet deliveries (four children survived in both cases), two quintuplet abortions, one late twin abortion, three normal single deliveries, one ectopic pregnancy, and one missed abortion. In our series only two cases of deep vein thrombosis were observed. In both of these cases, conception had not occurred.

There are reports of two severe cases of thromboembolic phenomena following HMG-HCG treatment which caused the death of one patient (carotid embolism) and a limb amputation in another. Brachial vein thrombosis in one patient and deep vein thrombosis in another were observed after induction of ovulation with HPG-HCG.

In our series, evidence of hemoconcentration with increased (6% to 10%) hematocrit values were observed in nine patients who showed increased serum osmolarity as well. Coagulation parameters such as clotting time, bleeding time, platelet count, prothrombin, and fibrinogen were found to be within normal limits. Phillips et al. studied the coagulation and fibrinolytic systems in the hyperstimulation syndrome and reported increased levels of factor V, platelets, fibrinogen, profibrinolysin, and fibrinolytic inhibitors, and increased thromboplastin generation.

In our patients who suddenly developed severe OHSS we were unable to demonstrate increased capillary permeability in the retinal vessels, using fluorescence fundus photography. Four patients required surgical intervention. Three cases had torsion of ovarian cysts with hemorrhage, and one had an ectopic pregnancy. The possibility of rupture of ovarian cysts or the presence of ectopic pregnancy resulting in intraperitoneal hemorrhage should always be considered. In the acute stage of OHSS, therefore, patients should frequently be monitored by measurement of blood pressure, central venous pressure, and serial estimation of hematocrit.

If surgery is necessary, it should be conservative. Cases of unnecessary bilateral oophorectomy, especially in the hands of physicians not
familiar with this syndrome, have been reported.\textsuperscript{40, 41} In patients with an acute abdomen, intravenous pyelography should be performed in order to rule out hydroureter, which may be associated with this syndrome.\textsuperscript{42}

In our series, the acute clinical manifestations of the severe form of OHSS disappeared within several days if there were no complications. When conception did not occur, the ovarian cysts subsided 20 to 40 days after the appearance of the clinical symptoms of hyperstimulation.

**HORMONAL STATE OF HYPERSTIMULATION SYNDROME**

In our experimental model of OHSS, increased levels of 17β-estradiol, progesterone, 17-hydroxyprogesterone, and testosterone were observed in the peripheral ovarian circulation.\textsuperscript{43} Abnormally high levels of urinary estrogens, pregnanediol, 17-hydroxyprogesterone, and pregnanetriol were found in cases of OHSS following HMG-HCG treatment.\textsuperscript{26, 44-47} High pregnanetriol levels were not influenced by adrenal suppression.\textsuperscript{48} Patients with OHSS have increased serum levels of 17β-estradiol, estrone, 17-hydroxyprogesterone, progesterone, testosterone, and Δ\textsuperscript{5} steroids.

The correlation between estrogen secretion and the appearance of OHSS is well recognized; a correlation was found between the preovulatory urinary estrogen levels and the incidence of severity of OHSS.\textsuperscript{49} Excessive stimulation of the ovaries by exogenous gonadotropin preparations increases ovarian steroidogenesis via the Δ\textsuperscript{5} pathway.\textsuperscript{50} A significant increase in serum testosterone levels has been noted.\textsuperscript{51}

High plasma levels of sulfate-conjugated androsterone and metabolites of progesterone as well as a massive increase in urinary androsterone and pregnanediol have been observed in cases of OHSS. The plasma concentration of the metabolites of progesterone in overstimulated subjects reached values of the order observed during the second and third trimesters of pregnancy.\textsuperscript{52} In our experience, the levels of HCG in urine in cases of OHSS associated with conception of a single fetus were similar to those of normal single pregnancies at the same time of gestation. Higher levels of HCG were observed in cases of OHSS associated with multiple pregnancy, as would be expected.

There has been controversy concerning the levels of steroid hormone concentration in pregnancies occurring after HMG therapy.\textsuperscript{10, 53, 54} Mishell et al.\textsuperscript{55} showed the similarity of steroid hormone levels in HMG-treated patients without OHSS and during normal pregnancy. Patients who developed OHSS associated with pregnancy had markedly elevated levels of 17-hydroxyprogesterone and progesterone. High 17β-estradiol levels remained elevated for about 1 month, until multiple follicular enlargement subsided. Levels of 17-hydroxyprogesterone fell within 2 months to those of normal pregnancy at the same stage of gestation, while progesterone levels remained elevated. Rabau et al.\textsuperscript{56} determined serial urinary steroids in patients with OHSS associated with pregnancy. The high levels of 17-ketosteroids, 17-hydroxycorticosteroids, and pregnanetriol declined at the end of the first trimester of pregnancy, i.e., at the time when corpus luteum or corpora lutea regress.

**PATHOGENESIS**

The main pathologic findings in severe hyperstimulation syndrome are multiple ovarian cysts of more than 10 cm in diameter, follicular cysts, corpora lutea, and severe edema of the stroma.\textsuperscript{57} Massive enlargement of the ovaries is accompanied by different degrees of acute body fluid shift, with ascites formation, hydrothorax, and sometimes anasarca. The sudden body fluid shift seems to be due to increased capillary permeability, especially of the ovarian vessels, as was demonstrated in our experimental studies with the use of intravenous Evans blue and pantamine sky-blue dyes.\textsuperscript{58} Our experimental model of the hyperstimulation syndrome in the rabbit has been reproduced by Knox\textsuperscript{59} and others\textsuperscript{60} who were able to block the manifestations by the concomitant use of antihistamine preparations.

The evidence that increased capillary permeability is the pathogenetic mechanism of severe ovarian hyperstimulation is supported by the fact that the values for electrolytes in blood and ascitic fluid are similar. This demonstrates that ascitic fluid has transudated. The cause of increased capillary permeability in OHSS is still not clearly understood.

There is experimental evidence in the rat and in the rabbit that excessive estrogens may cause increased capillary permeability of the uterus and ovarian vessels.\textsuperscript{61, 62} It is well known that in cases of OHSS high levels of estrogen are found in the serum, urine, and follicular fluid. On the other hand, it is known that the administration of high
doses of estrogens do not, by themselves, produce clinical hyperstimulation, and we were unable to produce this syndrome by administering huge doses of estrogen to female rabbits.\textsuperscript{63}

Abnormally high levels of various steroids in the serum were detected in cases of OHSS following HMG-HCG treatment. As mentioned above, it was confirmed in our previous series and by others that only after ovulation and corpus luteum formation does this syndrome develop.\textsuperscript{31} In experimental animals the syndrome is not prevented by hysterectomy or extraperitonealization of the ovaries.\textsuperscript{63} Moreover, OHSS cannot be induced in male animals or in men treated with large doses of HMG preparations.\textsuperscript{58} Therefore, it is assumed that the increased capillary permeability found in cases of OHSS is due to some excess of intermediate metabolites secreted by the ovary after HMG-HCG stimulation.

In recent experiments, we set out to determine whether prostaglandins are the "active substances" playing a role in the development of this syndrome. It was demonstrated that indomethacin, a blocker of prostaglandin synthesis, can prevent the fluid shift associated with the ascites, pleural effusion, and hypovolemia seen in this syndrome.\textsuperscript{64} It may be that the excessive estrogen produced by the large numbers of developing follicles also stimulates increased production of prostaglandins, which in turn may be responsible for the increased capillary permeability observed in OHSS.

Rapid body fluid shift in cases of ovarian hyperstimulation may lead to hypovolemia and hemoconcentration as evidenced by increased hematocrit values and serum osmolarity in cases reported by us and others.\textsuperscript{18, 57} When not corrected immediately, hypovolemia may lead to decreased renal perfusion, subsequently stimulating the proximal renal tubules to resorb salt and water, resulting in clinical manifestations of oliguria, electrolyte imbalance, and azotemia.\textsuperscript{11, 18} Urinary aldosterone levels were found to be markedly increased in several patients with OHSS. High levels of aldosterone may prevent an effective sodium diuresis once plasma volume and renal perfusion are restored following initial treatment.\textsuperscript{16, 11}

From the clinical point of view, the rapid body fluid shift may lead to hemoconcentration, increased blood viscosity, and finally to the thromboembolic phenomena which are associated with the syndrome.

**FACTORS INFLUENCING THE OCCURRENCE OF OHSS**

**Selection of Patients**

Patients requiring induction of ovulation with gonadotropin preparations have been classified into two main groups by the World Health Organization Scientific Group\textsuperscript{14} in order to facilitate evaluation of results of therapy and its complications.

**Group 1.** The first group consists of patients with primary or secondary amenorrhea, low levels of endogenous gonadotropin, and lack of endogenous estrogenic activity.

**Group 2.** The second group comprises patients with anovulation associated with various menstrual disorders whose urinary and serum gonadotropin levels are in the normal range and who have evidence of endogenous estrogenic activity.

Patients belonging to group 1 require a higher dose of gonadotropin and a longer period of therapy. The incidences of mild and severe OHSS in 621 treated cycles of patients belonging to group 1 were 5.5% and 0.6%, respectively, compared with 10.8% and 1.2% in 784 treated cycles in group 2.\textsuperscript{14}

The cumulative report by Thompson and Hansen\textsuperscript{15} on 1286 patients who had received 3002 courses of HMG-HCG showed that in 74 patients (257 treatment courses) with primary amenorrhea (group 1), no cases of hyperstimulation syndrome were recorded.

Other series, especially that of Nillius et al.,\textsuperscript{65} summarizing the results of 532 patients treated with HPG-HCG during the period 1960–1971, did not classify patients by the criteria of the World Health Organization Scientific Group\textsuperscript{14}; it is therefore difficult to draw conclusions on the relationship between OHSS and the method of selection of patients. It is noted that some women are hypersensitive to gonadotropin treatment and respond time after time with hyperstimulation. Caspi et al.\textsuperscript{16} reported an increased incidence of hyperstimulation in menstruating, ovulatory, infertile patients (group 2) treated with HMG-HCG.

Reports in the literature emphasize the increased incidence of hyperstimulation in patients with polycystic ovarian disease. The data of Thompson and Hansen,\textsuperscript{15} however, on 212 patients treated for 546 courses showed that the incidence in polycystic ovarian disease was similar to that in other diagnostic groups. In our series of 25 patients, 12 patients had polycystic ovarian disease as determined by endoscopy. In
six cases the disease was due to HMG treatment, in three it was due to clomiphene-HCG, and in three patients the syndrome developed after combined treatment with clomiphene and HMG. Patients with polycystic ovarian disease have adequate or even elevated levels of endogenous luteinizing hormone (LH), which may result in the relative sensitivity to HMG or even pituitary extract of FSH alone; these patients are categorized in group 2.

In view of the greater danger of OHSS in group 2, particular caution should be exercised before inducing ovulation in these patients. Care must be taken to exclude other endocrinopathies, especially syndromes associated with galactorrhea, which may be the cause of anovulation, and for which there exists specific therapy. We initially manage patients with polycystic ovaries with clomiphene citrate only. When conception is not achieved after at least six treatment cycles, whether or not an adequate response is obtained, HMG therapy is considered in spite of the potential risks of OHSS.

It should be remembered that the ovaries of some patients with polycystic ovarian disease are also more sensitive to the effect of clomiphene. Additionally, mild OHSS due to clomiphene therapy has been observed in patients who have previously undergone surgery for benign physiologically cystic ovaries. Thus, under these conditions, clomiphene should be administered with extreme caution and should never be given in the presence of an ovarian cyst.

The Effect of Different Regimens of Therapy

A variety of treatment schedules for gonadotropin administration has been devised.66-70 Nearly all of these schedules are based on the fact that treatment with HMG or HPG results specifically in follicular growth and maturation. Ovulation may then be induced by a triggering dose of HCG.

The major regimens employed have been evaluated in relation to the effectiveness and occurrence of adverse reactions.15

a: One-Dose Method. Administration of HPG or HMG in a single large dose on day 1 followed by HCG on day 10.

b: Overlapping, Uniform Daily Dose. Dose of HCG overlapping the gonadotropin treatment in the last 1 to 3 days, and sometimes continuing for 1 or 2 days after stopping the gonadotropin medication.

c: Not Overlapping, Uniform Daily Dose. Administration of HPG or HMG for 9 to 12 days, and HCG given for 1 to 3 days starting 1 or 2 days after gonadotropin therapy has been stopped.

d: Step Regimen. Descending or ascending daily dosage of HPG or HMG with HCG given at the end of gonadotropin therapy, either overlapping or not overlapping the gonadotropin administration.

e: Administration of gonadotropin on days 1, 4, and 8 followed by HCG on day 11.

f: Administration of gonadotropin alone.

g: Administration of HMG in combination with clomiphene citrate.

Regimens a, f, and g are relatively ineffective concerning ovulation and the pregnancy rate. Moreover, the incidence of OHSS after HMG administration alone and following combined HMG and clomiphene is not trivial, and was observed to be 0.5% and 2%, respectively.

A lower incidence of OHSS was observed in treatment schedules in which HCG therapy did not overlap HMG administration, using a uniform daily dose of HMG or following the step regimen.

It was concluded that the treatment schedule of choice was daily administration of two ampules of HMG for 9 to 12 days, followed by the injection of HCG 1 or 2 days after the last HMG injection. This resulted in only a 0.4 incidence of OHSS.15

Recently, two techniques of HMG or HPG administration have been in use. These have been labeled the variable14, 71-73 and the fixed dose74, 75 techniques. The variable technique has been used more commonly. HMG or HPG is usually given daily, with both dose and duration of administration being variable. The decision to terminate gonadotropin administration and to give HCG is made during the cycle by indirect estrogen indices, or by direct estrogen determination in urine or serum.

In the fixed technique, the predetermined dose of gonadotropin is administered in a single daily injection or on 3 alternative days (the 1/5/8 scheme74 or the 1/3/5 scheme75) followed by HCG 3 days later.

Butler75 has investigated estrogen secretion during various regimens and has compared the results with those observed during normal ovulatory cycles. The Butler scheme75 resulted in a rate of estrogen increase that closely imitated the mean rise in the normal cycle. When the results with this method were compared with those obtained after the standard daily dosage, there were no significant differences in the rate of pregnancies, but the incidence of OHSS in the
1/3/5 regimen was higher. It was found later that Butler's regimen is more economic, and the incidence of OHSS can be further reduced by estrogen monitoring.

We use the variable method in which the daily dosage and duration of therapy depend on the individual response. Preventive monitoring was used previously for assessment of estrogenic activity by indirect indices, and at present serial determinations of serum estradiol levels are performed. The advantages of this regimen, especially in group 1 patients, is that the appropriate effective dose for the individual patient is attained more rapidly, in spite of the narrow margin between effective therapy and OHSS. We believe that this approach maximizes the number of pregnancies achieved, while close monitoring enables almost complete control of severe OHSS.

With regard to clomiphene, a definite relationship has been observed between the duration of therapy and ovarian enlargement and the severity of OHSS. When a single course of clomiphene was administered for 3 days or less, only 2.7% of patients developed ovarian enlargement. Yet with a single course of 4 to 7 days' duration, the incidence was 5.4%. Multiple courses of 7 days resulted in a 7.8% incidence of mild hyperstimulation.

**Dosage of Gonadotropin**

Our animal studies revealed a direct relationship between the dose of HMG administered and the production of OHSS. It was found that the change in ovarian size, degree of capillary permeability, and the severity of ascites and pleural effusion were related to the dose of gonadotropin administered.

In clinical practice, it was demonstrated that by using HMG or HPG preparations, a positive dose-response relationship exists regarding ovulation and pregnancy rate. In addition, a direct, positive association between the gonadotropin dose and the probability of the occurrence of OHSS has been reported. Whereas in the individual patient OHSS is a consequence of overdosage of gonadotropin administered, depending on the endogenous gonadotropin secretion and the state of follicular development at the beginning of stimulation, when dealing with a group of patients, we found no such correlation. In order to prevent OHSS, therefore, and to achieve follicular growth and maturation, the dose of HMG and the duration of treatment should be determined during each course of treatment by daily monitoring of the ovarian response by clinical and chemical methods.

The reason for this discrepancy is that different dosage of HMG or HPG may be required by patients belonging to the same clinical group and, even in the individual patient, requirements may vary from cycle to cycle of the treatment course. Thus, dosage is determined during each cycle.

As mentioned above, we employed the variable, individualized regimen for gonadotropin treatment. Dose determination in fixed regimens is reported also.

**FSH-LH Ratio**

Animal studies have shown that pure preparations of FSH are not sufficient for completion of follicular maturation and that additional LH is required for maturation of the follicle before administration of HCG for triggering ovulation and corpus luteum development.

Studies conducted with HPG and HMG preparations containing various ratios of FSH-LH in order to evaluate the effectiveness of induction of ovulation and the occurrence of adverse reactions have been carried out. Crooke et al. found that treatment with a preparation with a high FSH-LH ratio causes less ovarian hyperstimulation. Neale and Bettendorf found some correlation between the incidence of ovarian enlargement and the FSH-LH ratio in both HPG and HMG preparations. Preparations with an FSH-LH ratio below 0.1 and above 5 seemed to elicit more ovarian enlargement than did those preparations having a ratio in the range of 0.1 to 5. Therefore, ovarian hyperstimulation might be eliminated by reducing the dosage of LH, especially in patients with polycystic ovarian disease.

Other studies, however, have indicated that the effectiveness of gonadotropin preparations, and the occurrence of OHSS, were not dependent on the FSH-LH ratio. It is considered that the benefit of altering the FSH-LH ratio is borderline, and in view of the practical difficulties of varying the FSH-LH ratio, this parameter has little clinical application at present.

**HCG Administration**

HCG administration is critical for the development or prevention of OHSS. It is well known that OHSS will not occur following the administration of HPG or HMG alone, except in sporadic cases. The dosage and timing of HCG varies from 1,000 to 25,000 IU or more, and from one to several
doses which can either overlap or not overlap the administration of HMG or HPG. It was found that ovulation rates were similar following any dosage of HCG but that the pregnancy rate was highest after 6,000 to 15,000 IU. The frequency of OHSS was lower in patients given 1,000 to 5,000 IU, or more than 25,000 IU, than in patients administered 6,000 to 25,000 IU. Data on the regimens of HCG which did not overlap HMG show a significantly lower incidence of OHSS than when HCG overlapped.15

It is well established today that by monitoring the estrogen levels daily during administration of HMG or HPG, and by withholding HCG when the estrogen levels are too high, severe OHSS can be prevented.

Patients treated with HMG show a continuous increase in serum estradiol for 24 to 48 hours after the last HMG injection. In spontaneous ovulatory cycles, values ranging from 200 to 400 pg/ml of estradiol were found in the middle of the cycle. In an attempt to mimic the normal changes during an ovulatory cycle, we administer HCG in a dosage of 10,000 IU, given in a single injection 24 to 48 hours after the last injection of HMG, when the serum estradiol levels are approximately 300 to 500 pg/ml. These values are slightly higher than those in a normal ovulatory cycle, but the probability of pregnancy is greater when "minimal" ovarian hyperstimulation occurs. The administration of HCG is withheld if the estradiol levels are more than 800 pg/ml, in order to prevent OHSS.

HCG administration for triggering ovulation can be substituted for purified human pituitary LH (HLH), given in repeated injections over a 24-hour period, mimicking the normal LH surge. HLH is able to maintain the corpus luteum and, by repeated injection, even to prolong its functional life beyond 14 days. No cases of severe OHSS were reported when HCG was substituted for HLH, but it should be remembered that the clinical usage of HLH is very limited. A case of quintuplet pregnancy after ovulation induction with HMG and HLH has been reported.82

LH-releasing hormone was clinically applied for the induction of ovulation, substituting for HCG. Of special interest, it has been suggested that the nasal application of LH-releasing hormone for induction of ovulation may reduce the incidence of OHSS.

**TREATMENT**

Mild and moderate hyperstimulation does not require any active therapy other than observation, whereas patients with severe OHSS require hospitalization and prompt treatment. On the premise that the basic disturbance in this syndrome is an acute shift of fluids from the intravascular compartment to the peritoneal and pleural cavities, management should be conservative, consisting essentially of monitoring plasma volumes and their correction (Fig. 1).

On admission, fluid intake and output are carefully assessed. Basal blood studies, including blood count and clotting parameters, are performed. Blood and urine osmolarity are measured. In more severe cases, blood volume estimations are carried out and central venous pressure is monitored.

In order to prevent hypovolemia—which may lead to hemoconcentration, decreased renal perfusion, and even shock—we infused our patients with low molecular weight dextran (Macrodex), 500 ml to 1000 ml/24 hours, and appropriate electrolytic solutions. In most cases, the infusion of low molecular weight dextran is continued for 4 to 7 days, with good results.

Diuretics are ineffective in evacuating fluid accumulated in the peritoneal and pleural cavities, and moreover are contraindicated, as a steeper decrease in the volume of the already contracted intravascular compartment may even induce hypovolemic shock. We do not, therefore, share the view of Shapiro et al., who recommended severe sodium and fluid restriction as the only treatment.

Anticoagulant therapy is indicated only in cases in which there is clinical evidence of thromboembolic phenomena, or laboratory findings of hypercoagulability. We have treated only three patients with heparin.

On the basis of our concept of prostaglandin mediation in OHSS, supported by our experimental animal model referred to above, indomethacin, a blocker of prostaglandin biosynthesis, was given to four patients with good results. One patient with the syndrome was pregnant. In-
domethacin may be contraindicated because of possible teratogenicity; nevertheless, we believe that indomethacin therapy is justified in severe OHSS, even if the patient has conceived.

In our opinion, abdominal paracentesis for drainage of ascites, as proposed by Rabau et al., should not be performed. Puncture of a large ovarian cyst present in this syndrome may cause intraperitoneal hemorrhage. Pleural effusions should be drained for respiratory distress, and sometimes repeated punctures are required. Surgical intervention should be avoided, the indications for surgery being either signs of intraperitoneal bleeding due to rupture of an ovarian cyst, or torsion of an ovarian cyst.

In our series, four patients required laparotomy. In two cases there was torsion of an ovarian cyst, the third case suffered peritoneal bleeding due to rupture of an ovarian cyst, and in the fourth case ectopic pregnancy was found.

If surgery is necessary in case of rupture of a cyst, it should be conservative, and only hemostatic measures should be undertaken in order to preserve gonadal tissue. Cases of acute abdomen have been submitted to laparotomy in which bilateral oophorectomy was performed.

MONITORING IN PREVENTION OF OHSS

The incidence of OHSS may be significantly reduced by clinical and laboratory methods used in monitoring gonadotropin therapy (Fig. 2). Today, the most widely used system of HMG therapy is the individualized treatment schedule. Ovarian response during the treatment course or courses may be followed by the following means:

1. Assessment of the optimal daily dose of HMG or HPG
2. Determination of timing of initiation of HCG or LH
3. Establishment of whether and when ovulation has taken place
4. Evaluation of corpus luteum function
5. Confirmation of conception

Since a direct observation of follicular maturation is impossible, indirect parameters have to be used. Successful stimulation of ovarian follicular maturation results in increasing production of estrogens. The luteal phase is characterized by the secretion of both estrogens and progesterone; therefore, measurement of these steroids can be used to assess the ovarian response to gonadotropin stimulation.

The optimal dose of gonadotropin required for induction of ovulation should produce a steroid pattern similar to that found during the spontaneous menstrual cycle. A satisfactory pattern consists of a slowly progressive increase in estrogen values under stimulation with HMG or HPG to a well-defined preovulatory peak, at which time HCG is administered. Estrogen values decrease after ovulation, and a second increase in estrogen levels with a concomitant increase in plasma progesterone or urinary pregnanediol levels should be obtained during the luteal phase.

At present, the estimation of the above steroids in plasma and urine is feasible in most medical centers. However, when gonadotropin preparations were introduced for clinical application, attempts were made to monitor gonadotropin therapy by indirect assessment of the effect of ovarian steroids on the vaginal epithelium, cervical gland secretion, or the endometrium. Vaginal cytology can be employed as a semiquantitative indicator of estrogenic activity by calculation of the karyopyknotic index. Evaluation of this method showed a good correlation between karyopyknotic index and urinary estrogen at the lower end of the scale, but as estrogen levels rise.

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**Fig. 2.** Monitoring of gonadotropin therapy.
to higher and more crucial ranges, the correlation becomes progressively poorer. Therefore, vaginal cytology has not been a successful method for monitoring gonadotropin therapy.\(^\text{89}\)

In our clinic, we have used the indirect method of assessment of estrogen activity by examination of the cervical score. This evaluation includes the quantity of cervical mucus, mucus crystallization (fern test), spinnbarkeit, and the changes in the appearance of the external cervical os. We found, as others have done,\(^\text{89}-\text{92}\) that the gradual development of copious mucus with maximal ferning and changes in the external os are good indicators of follicular ripeness. During treatment, the cervical parameters must be estimated frequently enough to determine the expected day of follicular maturation. It usually takes from 1 to 5 days from the initial cervical reaction until the follicular response to HCG by ovulation. The response, however, is semiquantitative only. A positive effect is already found at estrogen values of 10 to 20 μg/24 hours, whereas above 50 μg/24 hours there are no additional significant changes in the cervical score.

Individual responses of the endocervical glands may vary considerably. Some patients will respond with high cervical scores when the estrogen levels are still very low, while others will fail to respond at high estrogen levels. The sensitivity of an individual patient's endocervical glands may be determined by the administration of an estrogen preparation prior to gonadotropin therapy. In view of the above disadvantages of cervical scoring, this method is considered unsatisfactory; furthermore, the predictive value of impending ovarian hyperstimulation is poor.

Taymor\(^\text{21}\) was the first to report upon the correlation of high estrogen levels in urine and the appearance of OHSS. In our experience, this correlation is valid when a group of patients is considered, but in the individual case, there seems to be some disassociation between estrogen levels and the clinical findings. Subsequent reports have confirmed that estimation of estrogen levels in blood or urine have proved to be superior to the indirect methods when monitoring ovulation induction in order to minimize, if not completely prevent, complications.\(^\text{86, 89, 90, 94}\)

Older methods of measuring total or fractionated estrogens in urine permitted only retrospective assessment of the follicular response; thus OHSS resulted frequently. The introduction of rapid methods providing results of urinary estrogen measurement on the same day enables withholding the ovulatory dose of HCG or LH if the estrogenic response to HMG or HPG is excessive, and thus minimizes the risk of OHSS.\(^\text{85}\) Optimal preovulatory estrogen levels appear to be 50 to 150 μg/24 hours, as judged by high pregnancy rates.

Rabau et al.\(^\text{58}\) found that, when total estrogens were above 150 μg/24 hours, the incidence of hyperstimulation was increased. Jewelewicz et al.\(^\text{19}\) reported an incidence of hyperstimulation of 7.6% when the level of total estrogens measured was between 151 and 300 μg/24 hours; when estrogen levels were above 800 μg/24 hours, 90% of patients had hyperstimulation.

The development of sensitive, radiocompetitive binding techniques and radioimmunoassays for measuring plasma steroids has enabled more accurate assessment of ovarian response to treatment for induction of ovulation.

In our experience, as well as in that of other authors,\(^\text{96, 97}\) monitoring of patients undergoing treatment by measurement of plasma estradiol may permit a more direct and rapid assessment of follicular function. Although serum studies provide optimal control of therapy, practical difficulties are encountered because of the need for repeated blood sampling of patients and the requirement for greater laboratory expertise in serum determinations. Nevertheless, the advantage of measuring serum levels, which provide a measure of endogenous estradiol production on the same day as HMG administration, over determining urinary estrogens, which represent the previous day's levels, is seen as sufficiently important to justify the use of serum estradiol monitoring. Moreover, the reliability of urinary estrogen determination is impaired by the difficulties in urine collection and delivery to the laboratory.

In spontaneous ovulatory cycles, values ranging from 200 to 400 pg/ml were found in the middle of the cycle.\(^\text{95}\) In an attempt to mimic this normal pattern, we administer HCG when the serum estradiol levels are approximately 300 to 500 pg/ml. Administration of HCG is withheld if the estradiol levels are more than 800 pg/ml. When daily serum estradiol estimations were not available in our laboratory and indirect indices of monitoring HMG-HCG therapy were employed, patients who developed OHSS had levels which ranged from 1500 to 3000 pg/ml. Berquist et al.\(^\text{98}\) reported that cases of severe hyperstimulation were completely avoided by serum estradiol determination during 110 treatment courses with
OVARIAN HYPERSTIMULATION SYNDROME

HMG. The mean preovulatory serum estradiol level was 2430 pmoles/liter (range, 735 to 7000). When ovulation subsequently took place, mild hyperstimulation occurred in 6% of treatment cycles. During these cycles, the mean estradiol level at ovulation was 3130 pmoles/liter (range, 1490 to 4200).

Lehman et al.96 showed that in HMG-treated cycles there exists a preovulatory peak of 17-hydroxyprogesterone, as was demonstrated in spontaneous ovulatory cycles. They suggested that monitoring levels of 17-hydroxyprogesterone during gonadotropin therapy may be useful in addition to the measurement of estradiol to determine timing of HCG injection and for predicting the occurrence of OHSS. Nevertheless, recent studies in which levels of pregnanetriol (metabolite of 17-hydroxyprogesterone) were estimated during HMG treatment revealed that this parameter cannot substitute for monitoring estrogens in the prevention of OHSS.

The basic problem in monitoring ovulation induction with gonadotropin preparations is that the estrogen activity measured, by whatever method, is the sum of ovarian activity and represents one and usually more than one growing follicle. Moreover, the determination of preovulatory estrogen values does not necessarily reflect whether or not a Graafian follicle is suitable for ovulation induction with HCG. Nitschke et al.100 showed by a compound scan method with gray scale that direct observation of the number and size of stimulated follicles is feasible. This observation suggests that the ultrasonic method, in addition to previous clinical and laboratory methods, is desirable to reduce the incidence of hyperstimulation.

Finally, progesterone levels are also monitored in order to establish the occurrence of ovulation and the function of the corpus luteum. In OHSS, progesterone levels are increased above 30 ng/ml.

Early detection of conception in treatment with gonadotropins for induction of ovulation is important, and may be confirmed by β-HCG determination. OHSS associated with pregnancy has two implications: the clinical course may be more severe and prolonged, and the administration of an indomethacin should be avoided if not mandatory.

Even with the use of the most careful and painstaking preventive measures, it seems doubtful that hyperstimulation can be completely eliminated because of the narrow margin between ovulation induction dose and hyperstimulation induction dose.

SUMMARY

For the past two decades there have been important advances in the treatment of anovulation. The use of different preparations for the induction of ovulation, however, has given rise to several adverse reactions, the most important of which is the ovarian hyperstimulation syndrome (OHSS). The severe form of OHSS is characterized by gross ovarian enlargement, ascites, pleural effusion, and thromboembolic phenomena which are potentially lethal conditions. The main pathogenic mechanism is considered to be increased capillary permeability, especially of the ovarian small vessels, causing acute body fluid shift from the intravascular compartment to the peritoneal and pleural cavities. On the basis of an experimental model of OHSS, it is hypothesized that prostaglandins mediate this increased capillary permeability.

Factors affecting the incidence and severity of this syndrome are clinical conditions for which induction of ovulation is performed, pharmacologic preparations are used, and dosage and schedules of treatment are employed. Management is based on the concept of the pathogenetic mechanism and includes maintenance of intravascular volume by plasma volume expanders, reduction of capillary permeability, and prevention of thromboembolic phenomena. Surgical intervention is indicated only in cases of ovarian torsion or rupture and should be as conservative as possible.

The incidence of OHSS was high with the various preparations used in the initial period of this therapy. Since the introduction of monitoring of induction of ovulation by serial determination of urinary and plasma estrogens, the incidence and severity of OHSS have been improved. However, at present it is doubtful that OHSS can be completely avoided because of the existence of a relatively small margin of safety between successful induction of ovulation and the production of OHSS.

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