Distinction between early and late ovarian hyperstimulation syndrome


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Objective: To compare patient and cycle characteristics among three study groups: early ovarian hyperstimulation syndrome (OHSS), late OHSS, and non-OHSS.

Design: Prospective observational study.

Setting: University assisted conception service.

Patient(s): Women undergoing in vitro fertilization, intracytoplasmic sperm injection or gamete intrafallopian transfer treatment at Bristol University In Vitro Fertilization Service between January 1, 1995, and December 31, 1998.

Intervention: None.

Main Outcome Measure(s): Patient age, prevalence of polycystic ovaries, gonadotropin requirement, peak serum estradiol (E₂) concentration, number of oocytes retrieved, clinical pregnancy rate, number of gestation sacs, and severity of OHSS.

Result(s): Women with early OHSS had significantly higher serum E₂ levels and lower gonadotropin requirements than did the other groups. Cycles with either early or late OHSS had significantly more oocytes collected than those without OHSS. Serum E₂ and oocyte numbers did not accurately predict the risk of developing late OHSS. Clinical pregnancies occurred in all cycles with late OHSS, and multiple pregnancies were significantly more frequent in the late OHSS group than in the other groups. Late OHSS was more likely than early OHSS to be severe.

Conclusion(s): Early OHSS relates to “excessive” preovulatory response to stimulation, whereas late OHSS depends on the occurrence of pregnancy, is likelier to be severe, and is only poorly related to preovulatory events. (Fertil Steril 2000;73:901–7. ©2000 by American Society for Reproductive Medicine.)

Key Words: OHSS, IVF complications, severity, risk prediction.
can be predicted by conventionally used parameters of ovarian response may well differ.

This study was performed to distinguish the antecedent characteristics of assisted conception treatment cycles complicated by early or late OHSS. Other objectives were to examine the relationship between occurrence of pregnancy and the risk of early and late OHSS and to compare the severity of the two forms. The study also sought to clarify the predictive value of peak E₂ concentration and the number of oocytes retrieved in identifying cycles at risk of the two forms of OHSS.

MATERIALS AND METHODS

This was an observational study of anonymized data collected during cycles of IVF, intracytoplasmic sperm injection (ICSI), and gamete intrafallopian transfer (GIFT) treatment at the Bristol University IVF Service between January 1, 1995, and December 31, 1998. Individual patients gave consent for treatment. Patients also agreed that data from their treatment cycle would be stored in accordance with U.K. law.

Norethisterone (5 mg b.i.d.) was administered for 7 days beginning on the 19th day of the preceding cycle. Buserelin (600 μg) in daily divided doses was started 2 days later. Serum E₂ was measured at the onset of menstruation to confirm ovarian suppression. If the E₂ concentration was ≥160 pmol/L, purified FSH or hMG was administered by a standardized regime (5). Transvaginal ovarian ultrasound scan and serum E₂ were used to monitor follicular growth, starting on stimulation day 8 and repeated as appropriate.

The criterion for proceeding to hCG was the presence of three or more follicles 18 mm or larger, with an appropriate E₂ level (500–1,000 pmol/L per large follicle). If at the second scan the patient was not ready for hCG that day, but could be predicted to be ready within 2 days, hCG administration was arranged without further monitoring. If the E₂ concentration exceeded 15,000 pmol/L or the number of follicles ≥12 mm in mean diameter exceeded 30, the cycle was cancelled because of the perceived hyperstimulation risk. The luteinizing dose of hCG (Profasi, Serono, Welwyn Garden City, United Kingdom) was 5,000 units administered subcutaneously 36 hours before expected oocyte collection.

In patients undergoing IVF or ICSI treatment, up to three embryos were transferred 48 hours after insemination. A maximum of three oocytes were transferred to the fallopian tube in patients receiving GIFT treatment. In patients from whom more than 19 eggs were obtained or the peak E₂ level exceeded 10,000 pmol/L, progesterone suppositories 400 mg b.i.d. were administered for luteal support. Progesterone treatment continued for 2 weeks from the day of embryo transfer (ET) or the second day after GIFT. In all other patients, hCG (2,500 IU) was administered on the day of ET or the second day after GIFT, and again 5 days later.

Patients were told the symptoms of OHSS and asked to contact the unit in the event they developed abdominal distension or discomfort. Symptomatic patients were assessed to confirm the diagnosis and grade the severity of OHSS according to the criteria of Golan et al. (6). OHSS presenting 9 or fewer days after oocyte retrieval was classified as early OHSS; that presenting later was classified as late OHSS.

Patients were asked to perform a urine βhCG test if they had not menstruated 14 days after ET. Pregnancy was defined as the detection of a gestation sac by a transvaginal ultrasound scan performed 4 weeks after ET in women who had not menstruated before then. Multiple pregnancy was diagnosed when two or more intrauterine gestation sacs were visible on transvaginal scan.

Data Collection and Analysis

Data relating to patient and cycle characteristics and outcome were collected from our center’s contemporaneous computerized records. Cycles developing OHSS were identified prospectively during the course of the study. Multiple cycles in the same patient were analyzed as if they were statistically independent. The ages, gonadotropin requirements, numbers of oocytes, and peak E₂ concentrations of patients in the three groups (non-OHSS, early OHSS, and late OHSS) were compared using Kruskal–Wallis tests as implemented in the Arcus Biomedical software (Arcus Biomedical version 6.80; Medical Computing, Leeds, United Kingdom), followed by use of the multiple comparison procedure (7); a 5% significance level was used. Pregnancy rates among the three groups were compared using pairs of two-tailed Fisher’s exact tests because frequencies were considered too small for an overall χ² test. A Mann–Whitney U test was used to compare the severity of OHSS between the early and late groups.

Sensitivity and specificity were calculated for different cutoff levels of peak E₂ concentration and oocyte numbers, and for the risk of developing early and late OHSS. The level that minimized the sum of false-positive and false-negative rates was chosen as the optimum cutoff (i.e., sensitivity and specificity were given equal weight). For calculating the risk of developing early OHSS, the denominator included cycles without OHSS as well as those that developed late OHSS. For calculating the risk of late OHSS, the denominator included only cycles without OHSS. The positive likelihood ratio (LR+) and the negative likelihood ratio (LR−) were calculated for each optimum cutoff level. An LR+ of 10 or greater or an LR− of 0.1 or less was considered highly significant, and an LR+ between 5 and 10 or an LR− of 0.1 to 0.2 was considered moderately significant (8).

RESULTS

A total of 2,362 consecutive cycles of IVF, ICSI, or GIFT in 1,565 patients reached the stage of oocyte retrieval in the
study period. OHSS occurred in 78 cycles (3.3%) in 75 patients; early OHSS was seen in 48 cycles (2.03%); and late OHSS occurred in 30 cycles (1.27%). The median time of OHSS onset was 7 days after oocyte retrieval (range 2–21 days).

**Patient Characteristics**

An overall statistically significant difference was apparent among the three groups (early OHSS, late OHSS, and non-OHSS) in terms of patient age (overall $P = .04$) (Table 1). Patients with late OHSS were significantly younger than those without OHSS, but there was no statistically significant difference between patients with early OHSS and those without OHSS. Cycles with early OHSS were significantly more likely than cycles without OHSS to have a diagnosis of polycystic ovaries ($P = .003$) (Table 1).

**Parameters of Ovarian Response**

There was an overall statistically significant difference among the three groups in regard to the number of ampules of gonadotropin used (overall $P = .01$); significantly fewer ampules were used in cycles with early OHSS than in cycles without OHSS. No statistically significant difference existed between non-OHSS and late OHSS cycles in this respect (Table 1).

Peak E2 concentrations measured on the day of hCG differed among the three groups (overall $P < .001$); concentrations were significantly higher in cycles complicated by early OHSS than in cycles without OHSS or those with late OHSS. No statistically significant difference was apparent between peak E2 levels in cycles complicated by late OHSS and those without OHSS (Table 1). Similarly, differences in the number of oocytes retrieved (overall $P < .001$) were seen among the three groups. Significantly more oocytes were retrieved in cycles with either early or late OHSS than in cycles without OHSS. No statistically significant difference was apparent between the early and late OHSS cycles in this regard, however (Table 1).

Figure 1 shows the incidence of early and late OHSS for different ranges in the number of oocytes retrieved. The risk of developing early OHSS (expressed as a percentage of all cycles) rose with increasing numbers of oocytes retrieved (total $\chi^2$, $P < .0001$; $\chi^2$ for linear trend, $P < .0001$). The incidence of late OHSS (expressed as a percentage of all cycles minus those with early OHSS) also rose as the numbers of oocytes retrieved increased (total $\chi^2$, $P = .01$; $\chi^2$ for linear trend, $P = .0005$).

**TABLE 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-OHSS (n = 2,284)</th>
<th>Early OHSS (n = 48)</th>
<th>Late OHSS (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>34 (19–49)</td>
<td>34 (23–41)</td>
<td>32 (28–38)$^+$</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>93 (4.1%)</td>
<td>7 (14.6%)$^+$</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Ampules of gonadotropin used*</td>
<td>31.5 (10–164)</td>
<td>26 (13–60)$^+$</td>
<td>30 (16–72)</td>
</tr>
<tr>
<td>Oocyte numbers*</td>
<td>9 (1–37)</td>
<td>13 (6–41)$^+$</td>
<td>13 (5–27)$^+$</td>
</tr>
<tr>
<td>Day of hCG E2 (pmol/L)* (n = 1,212)</td>
<td>4,860 (944–22,097)</td>
<td>11,100 (3,030–15,600)$^+$ (n = 23)</td>
<td>6,610 (3,251–10,620) (n = 14)</td>
</tr>
</tbody>
</table>

*Note: OHSS = ovarian hyperstimulation syndrome; hCG = human Chorionic Gonadotropin; ET = embryo transfer.

* Median (range).  
† Statistically significant difference from non-OHSS ($P = .02$) by multiple comparison procedure after Kruskal-Wallis test.  
‡ Statistically significant difference from non-OHSS ($P = .003$) by Fisher’s exact test.  
§ Statistically significant difference from non-OHSS ($P < .01$) by multiple comparison procedure after Kruskal-Wallis test.  
¶ Statistically significant difference from late OHSS ($P = .04$) by multiple comparison procedure after Kruskal-Wallis test.  
All other comparisons were nonsignificant.

**FIGURE 1**

Incidence of early and late OHSS according to number of oocytes retrieved in the treatment cycle.

In 1,212 cycles, serum E\textsubscript{2} concentration was measured on the day hCG was administered. Early OHSS occurred in 23 (1.9%) of these cycles, and late OHSS was seen in 14 (1.2%). The incidence of early OHSS rose with increasing peak E\textsubscript{2} level, but the incidence of late OHSS showed no relationship to the peak E\textsubscript{2} level.

### Predictive Value of Peak E\textsubscript{2} Concentration and Oocyte Numbers

To determine the oocyte number and peak E\textsubscript{2} concentration that best distinguished between cycles with and without OHSS, sensitivity and specificity were calculated for a series of cutoffs. Table 2 shows the optimum cutoff values obtained by these calculations, and an analysis of their predictive abilities.

Calculations were performed separately for the following categories: all OHSS, moderate or severe OHSS, all early OHSS, moderate or severe early OHSS, and late OHSS. (All cases of late OHSS were moderate or severe; hence, only one calculation was performed for late OHSS.) A moderately significant positive likelihood ratio was obtained for an E\textsubscript{2} level in excess of 9,701 pmol/L in predicting early OHSS of any severity. None of the other positive likelihood ratios were significant. A moderately significant negative likelihood ratio was obtained for a peak E\textsubscript{2} level lower than 6,782 pmol/L in predicting the risk of moderate or severe early OHSS. None of the other negative likelihood ratios were significant.

### Pregnancy Rates

All cycles in which late OHSS occurred resulted in clinical pregnancies. Cycles in which late OHSS occurred were significantly more likely to result in clinical pregnancy than cycles without OHSS or those with early OHSS ($P<.001$). The clinical pregnancy rate did not differ significantly between cycles with early OHSS and those without OHSS (Table 3). Multiple pregnancies as a proportion of all cycles were significantly more likely to occur in cycles with late OHSS than in those without OHSS or with early OHSS ($P<.001$). The multiple pregnancy rate in cycles with early OHSS did not differ significantly from that in cycles without OHSS (Table 3).

### Number of Gestation Sacs

Non-OHSS cycles were excluded from this analysis if the patient was older than 39 years or had been diagnosed with hydrosalpinx. The mean ± SD of the number of embryos transferred did not differ significantly among the non-OHSS, early OHSS, and late OHSS groups (2.7 ± 0.58, 2.7 ± 0.44, and 2.8 ± 0.34, respectively).

Overall, a highly significant statistical difference in the

### TABLE 2

<table>
<thead>
<tr>
<th>Oocyte number</th>
<th>Optimum cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All OHSS</td>
<td>10</td>
<td>75</td>
<td>61</td>
<td>1.98 (1.68–2.22)</td>
<td>0.39 (0.26–0.56)</td>
</tr>
<tr>
<td>Moderate or severe OHSS</td>
<td>9</td>
<td>80</td>
<td>55</td>
<td>1.80 (1.51–2.01)</td>
<td>0.35 (0.20–0.57)</td>
</tr>
<tr>
<td>Early OHSS</td>
<td>10</td>
<td>81</td>
<td>61</td>
<td>2.10 (1.75–2.36)</td>
<td>0.30 (0.16–0.51)</td>
</tr>
<tr>
<td>Moderate or severe early OHSS</td>
<td>9</td>
<td>88</td>
<td>54</td>
<td>1.95 (1.56–2.15)</td>
<td>0.21 (0.07–0.52)</td>
</tr>
<tr>
<td>Late OHSS peak serum E\textsubscript{2}</td>
<td>8</td>
<td>83</td>
<td>47</td>
<td>1.57 (1.25–1.77)</td>
<td>0.35 (0.15–0.71)</td>
</tr>
<tr>
<td>All OHSS</td>
<td>6,359</td>
<td>81</td>
<td>65</td>
<td>2.29 (1.84–2.64)</td>
<td>0.29 (0.14–0.52)</td>
</tr>
<tr>
<td>Moderate or severe OHSS</td>
<td>6,359</td>
<td>76</td>
<td>64</td>
<td>2.12 (1.56–2.52)</td>
<td>0.37 (0.17–0.68)</td>
</tr>
<tr>
<td>Early OHSS</td>
<td>9,701</td>
<td>74</td>
<td>88</td>
<td>2.88 (1.96–3.28)</td>
<td>0.13 (0.02–0.55)</td>
</tr>
<tr>
<td>Moderate or severe early OHSS</td>
<td>6,782</td>
<td>91</td>
<td>69</td>
<td>6.37 (4.48–8.13)</td>
<td>0.29 (0.14–0.52)</td>
</tr>
<tr>
<td>Late OHSS</td>
<td>4,498</td>
<td>86</td>
<td>46</td>
<td>1.57 (1.10–1.79)</td>
<td>0.31 (0.08–0.87)</td>
</tr>
</tbody>
</table>

*Note: Positive likelihood ratios $\geq 5$ and negative likelihood ratios $\leq 0.2$ are in bold.

* pmoL/liter.


### TABLE 3

| Pregnancy rates in cycles with early or late OHSS and without OHSS. |
|--------------------------|--------------------------|--------------------------|
|                          | Non-OHSS ($n = 2,284^*$) | Early OHSS ($n = 48$) | Late OHSS ($n = 30$) |
| Not pregnant (%)         | 1,668 (73%)              | 35 (72.9%)              | 0                      |
| Clinical pregnancies (%)  | 557 (24.4%)              | 13 (27.1%)              | 30 (100)$^+$           |
| Multiple pregnancies (%)  | 176 (7.7%)               | 3 (6.3%)                | 16 (53.3)$^+$           |

* Includes 59 biochemical pregnancies.

$^+$ Statistically significant difference from both non-OHSS and early OHSS ($P<.001$) by Fisher’s exact test.

All other differences nonsignificant.

number of gestation sacs was apparent among the three groups \((P<.001)\); significantly more gestation sacs appeared in cycles with late OHSS \((1.67 \pm 0.34)\) than in those with early \((0.36 \pm 0.67)\) or no OHSS \((0.37 \pm 0.68)\; all values are mean \pm SD). No significant difference was apparent between cycles with early OHSS and those without OHSS in this regard. The risk of late OHSS rose when the number of gestation sacs increased \((\text{total } \chi^2, P<.001; \chi^2 \text{ for linear trend, } P<.001)\). The risk of early OHSS was not significantly affected by the occurrence of pregnancy or the number of gestation sacs \((\text{total } \chi^2, P=.7; \chi^2 \text{ for linear trend, } P=.5)\).

**Severity of Early and Late OHSS**

Late OHSS was significantly more likely to be severe than early OHSS \((P<.0001\) by the Mann-Whitney \(U\) test). In cycles that resulted in conception, OHSS was appreciably more likely to be severe than in those not ending in conception \((P<.001\) by Mann-Whitney \(U\) test). The OHSS became more severe as the number of gestation sacs increased \((\text{Kendall’s } \tau = 0.559; \text{ two-tailed } P<.001)\).

**DISCUSSION**

Dahl Lyons et al. \((1)\) postulated that OHSS occurs in its early and late forms as distinct clinical entities with differing risk factors. They observed six cases of moderate or severe OHSS presenting 3–7 days after the ovulatory injection of hCG. In these patients, the number of oocytes retrieved and the serum E2 concentration on the day of hCG injection were significantly higher than in patients who did not develop OHSS. These investigators also observed severe OHSS with an onset 12–17 days after ovulatory hCG injection in four women with multiple pregnancies. Peak E2 levels and oocyte numbers did not differ appreciably between these patients and those without OHSS.

This finding led the investigators to postulate that patients who developed OHSS 3 to 7 days after ovulatory hCG injection were a group distinct \(\text{i.e., “early” OHSS}\) from those who developed OHSS 12 to 17 days after ovulatory hCG injection \(\text{i.e., “late” OHSS}\). Our study sought to determine whether such a distinction could be made and, if so, to further distinguish the antecedent cycle characteristics of “early” and “late” OHSS.

The first issue to be resolved was the precise time of onset that demarcates early from late OHSS. In this study, OHSS onset was observed on all days between 2 and 16 after oocyte retrieval. In one case, onset of OHSS occurred 21 days after oocyte retrieval. Of the smaller number of cases studied by Dahl Lyons et al. \((1)\), none exhibited OHSS onset between 8 and 11 days or more than 17 days after ovulatory injection of hCG. Hence, generalizing their criteria to this study would leave us with a group of patients who could not be classified as either “early” or “late.” However, the crux of the investigators’ argument was the distinction between endogenous and exogenous hCG as the potential initiator of OHSS, with “late” OHSS resulting from endogenous hCG in cases of an implanting multiple pregnancy. This distinction was taken into account when the two study groups were defined.

The luteal support regime for patients in this study consisted of hCG administered 2 and 7 days after oocyte recovery. It was considered unlikely that OHSS having an onset 3 or more days after the second hCG injection could have been caused by the exogenously administered hCG. Therefore, OHSS with onset 10 or more days after oocyte retrieval was considered “late” OHSS. This agrees with the definition of late OHSS established by Dahl Lyons et al. \((1)\), who stated that late OHSS occurs 12 or more days after the ovulatory injection of hCG. Any OHSS with onset before 12 days was classified as “early” OHSS. The day of oocyte retrieval, rather than the day of hCG administration, was used for this distinction because these patients received the ovulatory dose of hCG in the late evening, whereas oocytes were retrieved in the morning.

The results of this study suggest that OHSS occurs in “early” and “late” forms as defined earlier. These forms differ in their patient characteristics, ovarian response parameters in the antecedent treatment cycle, relationship to pregnancy, and clinical severity. Patients with late OHSS were significantly younger than patients without OHSS. The importance of this finding may lie in the association of late OHSS with pregnancy. The Belgian multicentric study \((9)\) also noted younger age in OHSS patients compared to non-OHSS controls, although that study did not distinguish between the early and late forms.

Patients with early OHSS were significantly likelier to have a diagnosis of polycystic ovaries than those without OHSS. Delvigne et al. \((9)\) noted that features suggestive of polycystic ovary syndrome (PCOS), including hyperandrogenism, anovulation, and an LH/FSH ratio greater than 2, were more prevalent among OHSS patients than in non-OHSS controls.

In this study, polycystic ovaries were diagnosed when typical features appeared on a transvaginal ultrasound scan. MacDougall et al. \((10)\) reported polycystic ovaries diagnosed by ultrasound in 63% of severe OHSS cases and in 57% of moderate OHSS cases compared with 33% for the general patient population. Ultrasonically diagnosed polycystic ovaries are associated with an excessive ovarian response and a greater risk of OHSS, even in the absence of clinical features of PCOS \((11)\).

Ovarian response parameters differed significantly between cycles with early OHSS and those without OHSS. Peak E2 levels and numbers of oocytes retrieved were higher in early OHSS cycles than in those without OHSS. This finding suggests a greater ovarian response in cycles where early OHSS developed. Our conclusion agrees with the findings of MacDougall et al. \((10)\) and Delvigne et al. \((9)\).
although their studies did not consider the time of OHSS onset. The number of gonadotropin ampules required in early OHSS cycles was significantly less than that required in cycles without OHSS. Together with the higher peak $E_2$ levels, this suggests a greater ovarian sensitivity to gonadotropin stimulation in cycles complicated by early OHSS.

The higher incidence of polycystic ovaries in the early OHSS group, compared with the non-OHSS group, is in accordance with the well-recognized higher ovarian sensitivity of women with polycystic ovaries. MacDougall et al. (10) found no difference between severe OHSS cases and controls in terms of the number of gonadotropin ampules required. This lack of distinction may be due to the smaller number of cases in their series (15 OHSS cases and 1,287 controls) and the fact that their study did not consider early and late OHSS cases separately. Delvigne et al. (9), in their study of 128 OHSS cases and 256 controls, described a lower gonadotropin requirement and higher peak $E_2$ levels in the OHSS cases. They also described a steeper slope of rise in serum $E_2$ levels during stimulation in OHSS cases, once again indicating heightened ovarian sensitivity.

Cycles with late OHSS did not differ significantly from cycles without OHSS in their peak $E_2$ levels and gonadotropin requirements. This finding indicates that ovarian sensitivity and response did not differ appreciably between these two groups, in contrast to cycles with early OHSS. However, the number of oocytes retrieved was higher in cycles where late OHSS developed subsequently than in cycles without OHSS. This finding is in contrast to that of Dahl Lyons et al. (1) and may seem difficult to interpret relative to the other parameters of ovarian response. One possible explanation is that the higher oocyte numbers in cycles with late OHSS reflect a larger number of ovarian follicles and, consequently, a larger cohort of granulosa cells available to be stimulated by luteal hCG.

The number of ovarian follicles developing in response to stimulation was not used as a parameter in this study. Although investigators have described a correlation between increased numbers of follicles and the risk of OHSS (12), the measurement of follicle numbers and sizes is subjective, and results may be difficult to reproduce. Asch et al. (3) observed a good correlation between the number of follicles and the number of oocytes collected.

Late OHSS was strongly associated with pregnancy and was restricted to cycles in which clinical pregnancy occurred. The initial report suggesting that OHSS occurs in two distinct forms defined by time of onset (1) described late OHSS in cycles with multiple gestation only. However, the findings of our study show that late OHSS is associated with both singleton and multiple pregnancy. This association was stronger for multiple pregnancies than for singleton pregnancies. The risk of developing late, but not early, OHSS rose significantly when the number of gestation sacs increased. Levels of hCG in multiple pregnancies tend to be higher than in singletons from a very early gestation stage, although there is considerable overlap (13, 14). Also, the hCG level required to precipitate OHSS may vary from one individual to another, and may relate to each individual’s unique cytokine profile (15).

It is not possible from the present study to draw conclusions about the effect of luteal phase support on the incidence of OHSS. This study was not designed to be a comparative trial of different luteal support methods, and our clinical protocol was such that cycles receiving hCG luteal support exhibited ovarian response parameters significantly different from those not receiving hCG.

Late OHSS was much likelier than its early counterpart to be clinically severe. This finding may reflect a greater magnitude and longer duration of granulosa cell stimulation in late OHSS, as a result of its association with pregnancy. The fact that OHSS severity increases with the number of gestation sacs, irrespective of the time of onset, strengthens this hypothesis.

The risk of early OHSS rose with increasing preovulatory serum $E_2$ concentrations, suggesting that the magnitude of preovulatory ovarian response to stimulation is an important determinant of this complication. In contrast, the risk of late OHSS was not related to peak $E_2$ levels. The risk of both early and late OHSS rose when the numbers of oocytes retrieved increased, although this observation was more pronounced for early than for late OHSS.

Sensitivity and specificity were calculated for a number of cut-off values. These calculations helped determine the optimal cutoff for the number of oocytes retrieved and peak $E_2$ concentrations for distinguishing between cycles with and without OHSS. The optimal value chosen was that which minimized the sum of the false positives and false negatives. The likelihood ratios for the optimal cutoff values derived by this analysis were uniformly poorer for late OHSS than for early OHSS. Highly significant likelihood ratios were not obtained for any of the optimum cutoff levels in predicting the risk of either early or late OHSS. Moderately significant likelihood ratios were obtained for peak $E_2$ levels $>9,701$ and the risk of early OHSS (LR $+ 6.37$), as well as for peak $E_2$ level $<$ $6,782$ and the risk of moderate or severe early OHSS (LR $- 0.14$). Neither oocyte number nor $E_2$ concentration reached significant levels in predicting the risk of late OHSS.

Existing literature does not describe the extent to which indices of ovarian response, such as the peak serum $E_2$ concentration, the number of ovarian follicles, and the number of oocytes retrieved, can predict the two forms of OHSS. From our research, it appears that the two forms of OHSS differ in the extent to which they can accurately be predicted by these indices.

Late OHSS can only be poorly predicted by criteria relating to ovarian response, especially peak $E_2$ concentra-
tions. This observation might explain part of the discrepancy observed between studies using similar criteria to predict the risk of OHSS (3, 4) and the occurrence of severe OHSS in apparently “low-risk” cycles. Delvigne et al. (16) reported that 33% of severe OHSS cases occurred in cycles without obvious risk factors in terms of infertility diagnosis or ovarian response. Despite this finding, ovarian response parameters are widely used to identify cycles for measures intended to prevent OHSS. E₂ concentrations and follicle numbers are used in practice to cancel, or delay, hCG administration (17). Trials of new preventative measures have concentrated on women who, on the basis of arbitrary ovarian response criteria (18, 19), are believed to be at risk for OHSS. However, restricting preventative measures to cycles with E₂ concentrations above a certain arbitrary level would not eliminate late OHSS.

The greater severity of late OHSS and its poor correlation with conventional ovarian response parameters highlight this condition as a major problem in clinical practice. It follows that preventative strategies based on criteria derived from ovarian response indices would be of limited use in preventing those OHSS cases that are likelier to experience the worst disease.

A rise in serum vascular endothelial growth factor (VEGF) level occurring between the day of hCG administration and the day of oocyte retrieval has been suggested as a possible marker of OHSS risk (20). However, this study appears to have included only those OHSS cases where onset occurred within 7 days of ET (i.e., “early” OHSS).

Ludwig et al. (21) compared free serum VEGF levels in 10 women developing severe OHSS and in 15 controls without OHSS. A cut-off level of 200 pg/mL on the day of hCG administration yielded a positive predictive value of 75% and a negative predictive value of 92%. Although the time of OHSS onset among the patients in this study is not specified, the possible predictive role of free VEGF levels merits further investigation in a defined patient group.

In summary, this study supports the hypothesis that OHSS occurs in two forms, distinguished by time of onset. Early OHSS relates to ovarian sensitivity and the magnitude of preovulatory ovarian response to stimulation. Late OHSS is only poorly related to the ovarian response; it may relate instead to the magnitude of endogenous hCG stimulation from implanting gestation(s). Late OHSS is more likely to be severe than the early form. It is also more difficult to predict from criteria relating to ovarian response. Research on predictive and preventative strategies should consider the different characteristics of these two forms of OHSS.

References