

# An eight year review of hospitalization for ovarian hyperstimulation syndrome

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## Summary

We analyzed the etiologic factors and trends of hospitalization for ovarian hyperstimulation syndrome (OHSS) resulting from the use of fertility medications. From May, 1986 through April, 1994, patients hospitalized with OHSS were exclusively admitted to the University Hospital. Analysis was performed with regards to treatment method, severity of hyperstimulation, and onset of disease. Overall, 14 patients were hospitalized for a rate per cycle of 0.1% (14/14, 283). The rate of admission for patients undergoing superovulation (9/12, 945; .07%) was significantly lower than for those undergoing assisted reproductive techniques (ART) (5/1, 338; .37%). The total number of injectable gonadotropin ampules used was also higher in patients admitted following ART versus superovulation. A significantly greater number of patients presenting with late developing hyperstimulation syndrome (5/7; 71.4%) manifested severe disease as opposed to those hospitalized with early onset OHSS (1/7; 14.3%).

Our data suggest that hospital admission is an infrequent event following the use of fertility medications, and patients are more likely to be hospitalized with OHSS following ART than superovulation.

**Key words:** Hospitalization; Ovarian hyperstimulation syndrome.

## Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic complication from the use of ovulatory stimulation agents in women with infertility. It is characterized by significant ovarian enlargement and fluid shifts from the intravascular to extravascular compartment in the luteal phase or in early pregnancy [1]. In its most severe forms, the syndrome can lead to electrolyte disturbances, thromboembolic events, acute respiratory distress syndrome, renal failure, and even death [2]. A number of authors have classified OHSS according to its severity [3-5]. The overall incidence varies for different degrees of the syndrome – namely 0.005 to 7% for moderate and 0.008 to 10% for its severe forms [5]. Another method of classification was recently proposed by Dahl Lyons *et al.* who distinguished between an early (day 3-7 after administration of hCG) and late (day 12-17 after hCG) form of this entity [6].

With the increasing use of ovarian stimulation, a significant change in the pattern of multiple births has occurred [7]. Similarly, some authors feel that the incidence of OHSS should increase as ovarian superstimulation becomes more widely available [8, 9]. On the other hand, advances in the methods of monitoring gonadotropin therapy may have helped to prevent a rising incidence of this syndrome [5]. Since it may not only lead to temporary disability but also to hospitalization with a related increase in health care expenditure, we were interested in analyzing the extent of hospital admission with OHSS over an extended time period. In addition, we wanted to examine whether the number of patients undergoing assisted reproductive techniques (ART) versus superovulation were equally affected.

## Materials and Methods

We analyzed all patients admitted with ovarian hyperstimulation syndrome from our Infertility program to the Robert Wood Johnson University Hospital between May, 1986 – April, 1994. Patients admitted specifically for adnexal torsion in early pregnancy following menotropin therapy have been previously reported [10] and were excluded, since without torsion, these patients would not have been hospitalized with OHSS. During this time, 12,945 superovulation cycles and 1,338 assisted reproductive technology cycles were performed.

Treatment for superovulation consisted of clomiphene citrate/human menopausal gonadotropins (Serophene/Pergonal and/or Metrodin, Serono Laboratories, Norwell, MA), or gonadotropins alone followed by hCG 10,000 IU intramuscularly (IM). Subsequently, patients underwent intercourse or intrauterine insemination if indicated due to male and/or cervical factor infertility. Assisted reproductive technology cycles consisted of ovarian stimulation with Pergonal/Metrodin, usually preceded by hypothalamic-pituitary-ovarian down-regulation with a GnRH agonist (leuprolide acetate, TAP pharmaceuticals, Deerfield, IL). Subsequent to injection of 10,000 IU hCG, oocyte retrieval was performed, and was followed by eventual uterine (embryo), or intrafallopian (gamete or zygote) transfer. The luteal phase was supported with hCG (2500 IU IM administered once, 7-10 days after the initial dose), or progesterone vaginally (50-100 mg twice daily) or intramuscularly (50 mg once daily). Women with signs or symptoms suggestive of OHSS were evaluated clinically, and managed with a protocol involving the withholding of hCG for luteal phase support, sexual abstinence, increased frequency of monitoring based on individual circumstances, and incremental limitations on physical activity to the point of complete bedrest at home. Patients were hospitalized if they were: a) unable to be managed with this regimen, b) incapacitated by their symptoms, or c) experiencing worsening medical manifestations of hyperstimulation.

Superovulation and ART patients were analyzed as separate groups since ART stimulation cycles generally aim for a larger number of oocytes. Furthermore, ART cycles were characterized by the use of a GnRH agonist and by aspiration of follicles, which have been described as somewhat protective against the development of OHSS [11]. The impact of these divergent interventions could therefore be scrutinized in comparison to superovulation therapy. In addition, we analyzed an early versus late developing form of OHSS, comparing events within 10 versus more than 10 days following hCG administration.

Statistical analysis was performed by using Fisher's exact test for comparison of incidence and relative severity of OHSS, and the pregnancy/miscarriage rates in the superovulation versus ART groups. This test was also used to compare the percent of early versus late developing hyperstimulation syndrome with respect to treatment modality, severity of OHSS, and ultimate pregnancy outcome. The Wilcoxon rank sum test and student test were used to compare etiologic variables between superovulation and ART cycles. A P value less than 0.05 was considered significant.

## Results

During the eight year span, 14 patients were hospitalized with ovarian hyperstimulation syndrome. Thirteen were admitted due to significant abdominal pain, and one was admitted due to respiratory compromise. Other signs and/or symptoms found in these patients included nausea/vomiting (n=5), constipation (n=3), abdominal distension (n=2), fever (n=1), dizziness (n=1), significant (>10% of body weight) weight gain (n=2), and pelvic pain (n=1). Five women had undergone assisted reproductive technology procedures (gamete intrafallopian transfer – 3, in vitro fertilization – 2), and the remaining nine underwent superovulation with intrauterine insemination. Of these nine, five had received a sequential Serophene-Pergonal/Metrodin regimen, while four had received Pergonal/Metrodin therapy alone. The overall hospitalization rate per cycle was 0.1% (14/14,283); for patients undergoing ART it was 0.37% (5/1,338), whereas for those undergoing superovulation this rate was significantly ( $P<0.0006$ ) lower at 0.07% (9/12,945).

Table 1 shows the demographic data from both patient groups. No significant difference ( $P>0.05$ ) in age, body mass index, cycle day of hCG administration, number of follicles <14 mm or  $\geq 14$  mm in diameter, or estradiol level before hCG administration was found between the two groups. A significantly ( $P<0.03$ ) higher total number of Pergonal/Metrodin ampules was administered to patients undergoing ART ( $22\pm 5$ ) compared with those who underwent superovulation ( $12.8\pm 8$ ).

The overall pregnancy rate in our hospitalized patients was 50% (7/14). Clinical pregnancy rates were similar in the ART patients (4/5; 80%) compared with those who underwent superovulation (3/9; 33.3%) ( $P>0.05$ ). In addition, there was no significant difference ( $P>0.05$ ) in the miscarriage rates between the ART (2/4; 50%) and superovulation (1/3; 33%) groups.

Upon analyzing the severity of OHSS in these hospitalized patients, it was noted that eight of the 14 (57.1%) patients had moderate, while the remaining six (42.9%) had the severe form as defined by Golan's criteria [5]. The relative rates of moderate and severe hyperstimula-

tion syndrome between the ART group (two moderate, three severe) and the superovulation group (six moderate, three severe) were not significantly different ( $P>0.05$ ). One patient who underwent an ART cycle developed minimal hydronephrosis which resolved with bedrest. Another patient who was admitted due to OHSS following superovulation therapy subsequently developed a right ovarian torsion which necessitated laparotomy and reposition of the ovary. Three patients experienced a 10-12% rise from baseline in their hematocrit levels, however no patient developed severe hemoconcentration (hematocrit>45%). In addition, there were no cases of significant electrolyte, platelet, or coagulation profile abnormalities.

Table 2 reveals a breakdown of hospitalized patients who presented with an early ( $\leq 10$  days after hCG) versus late ( $>10$  days after hCG) developing form of OHSS. No significant difference ( $P>0.05$ ) in the rates of clinical pregnancy, viable pregnancy, or miscarriage was seen between the two forms. In addition, the relative number of superovulation and ART cycles was not significantly different ( $P>0.05$ ) for patients presenting with early versus late developing OHSS. However, with respect to severity, it was found that a significantly ( $P<0.05$ ) higher percentage of patients presenting with late developing OHSS manifested the severe form as opposed to those hospitalized with early OHSS (Table 2).

Table 1. — Demographic data of patients hospitalized with ovarian hyperstimulation syndrome following assisted reproductive techniques or superovulation (mean  $\pm$  SD)

	Assisted reproductive techniques	Superovulation
Age (years)	34.8 $\pm$ 5.0	32.3 $\pm$ 5.2
Body Mass Index (kg/m <sup>2</sup> )	28.0 $\pm$ 0.8	26.1 $\pm$ 2.7
No. of Pergonal and/or Metrodin ampules given	22.0 $\pm$ 5.0*	12.8 $\pm$ 8.0*
Cycle day of hCG administration	13.6 $\pm$ 3.4	11.5 $\pm$ 3.7
No. of follicles		
$\geq 14$ mm	11.6 $\pm$ 3.4	9.0 $\pm$ 3.3
$\leq 14$ mm	5.6 $\pm$ 1.8	6.0 $\pm$ 2.3
Estradiol level before hCG (pg/ml)	1200 $\pm$ 268.3	1112 $\pm$ 439.4

\* $P<0.03$

Table 2. — Patients presenting with early ( $\leq 10$  days after hCG) versus late ( $>10$  days after hCG) developing ovarian hyperstimulation syndrome

	Early Syndrome	Late Syndrome
Total No. of patients	7	7
Clinical pregnancies	2	5
Viable pregnancies	0	3
Miscarriages	2	2
Treatment cycles		
Superovulation	5	4
Assisted reproductive techniques	2	3
Severity of ovarian hyperstimulation syndrome		
Moderate	6	2
Severe	1*	5*

\* $P<0.05$

## Discussion and conclusions

While the precise pathophysiology of the ovarian hyperstimulation syndrome remains to be elucidated, evidence points to an increase in activity of the renin-angiotensin aldosterone systems which may affect capillary permeability and result in fluid shifting [8]. The identification of women at high risk for developing this syndrome is a crucial step in its prevention. For example, it is well recognized that patients with polycystic ovarian syndrome are more at risk [8]. During treatment, patients with higher serum estradiol levels [8, 12] and larger numbers of follicles at the time of hCG injection [13] are more likely to develop this disorder. In patients at high risk, withholding hCG can forestall the development of OHSS. Several therapeutic interventions have been proposed for the treatment of this syndrome [9, 11, 14-22]. These include follicular aspiration [11, 22], as well as the administration of intravenous albumin [14, 15], glucocorticoids [16], dopamine [17], antihistamines [18, 19], and GnRH agonists [9, 20, 21]. Irrespective of these therapeutic modalities, bedrest and ultimately hospitalization with fluid management and symptomatic relief measures are mainstays in the management of OHSS.

Our analysis indicated that the overall risk of hospitalization following superovulation or assisted reproductive techniques was low. Patients who underwent ART cycles were more likely to develop disabling OHSS that required admission than those who underwent superovulation cycles. This may be due to the fact that our target points for hCG administration differed between the two groups. In general, ART patients had no upper limit of estradiol level beyond which hCG was withheld, whereas those undergoing superovulation had hCG withheld if their estradiol level was >1,800 pg/ml. In addition, ART stimulation cycles aimed for a larger follicular recruitment as opposed to superovulation cycles, in which a more limited number of follicles was desirable. It was evident from our study that the effect of follicle aspiration was not sufficient to counteract the effect of increased stimulation in ART patients.

Our data are consistent with the observation that patients who develop the more severe forms of OHSS generally have higher clinical pregnancy rates than those who do not [23, 24]. All hospitalized patients presented with moderate to severe disease, and since exogenous or endogenous (pregnancy-derived) hCG is generally accepted as a factor in perpetuating OHSS [25], it was not surprising that 50% of our hospitalized patients were pregnant. With respect to the onset of development, we found that patients with late developing OHSS demonstrated a significantly higher rate of severe disease. Again, this may have been due to endogenous hCG from an early gestation exacerbating the effects of the initial, ovulatory hCG dose.

As the use of gonadotropin therapy increases, one can expect an increment in patients who will develop OHSS and require hospitalization. Overall hospitalization rates during an 8 year period, however, remained low in our

experience. Clinically, this supports the notion that the recent increase in gonadotropin use is balanced to some degree by concurrent advancements in monitoring and therapeutic techniques for OHSS, thus preventing a significant rise in hospital admissions.

In summary, our eight year review of hospitalized cases for ovarian hyperstimulation syndrome revealed that patients who underwent assisted reproductive technology cycles were at a higher risk for subsequent admission than those who were treated with superovulation. Management protocols differed between these therapies and thus may explain this difference. Patients admitted with the late onset form (>10 days after hCG dosage) were more likely to present with severe ovarian hyperstimulation syndrome. Overall, hospital admission with OHSS appears to be an uncommon event following the use of fertility medications.

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