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I

CLASSIFICATION OF OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome (OHSS) is characterized by bilateral, multiple follicular and thecal lutein ovarian cysts (Figure I.1) and an acute shift in body fluid distribution resulting in ascites (Figure I.2).

THE PURPOSE OF OVARIAN HYPERSTIMULATION SYNDROME CLASSIFICATIONS

The objectives of all OHSS classifications are three-fold (Aboulghar and Mansour, 2003). The first objective is to compare the incidence of OHSS. The second objective is to evaluate the efficacy of the different approaches for prevention of the syndrome. The final objective is to plan the management of OHSS, according to its severity and the presence or absence of complications.

OVERVIEW OF OHSS CLASSIFICATIONS

There has been no unanimity in classifying OHSS, and divergent classifications have made comparisons between studies difficult (Rizk, 1993). Aboulghar and

Fig. I.1: Multiple follicular cysts in the ovaries of a hyperstimulated patient

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Fig. I.2: Ascites in a hyperstimulated patient

Mansour (2003) have reviewed the classifications used for OHSS over the last four decades (Table I.1).

A group of pioneers in ovulation induction observed what they called adverse events in the first 100 patients undergoing ovulation induction (Rabau et al., 1967). This led them to propose the first classification of OHSS. This was later reorganized by Schenker and Weinstein (1978) into three main clinical categories and six grades. Golan et al. (1989) introduced a new classification of three categories and five grades of OHSS. This was later modified by further dividing the severe form into two subgroups (Navot et al., 1992). The most recent classifications with further modifications were introduced in 1999 by Rizk and Aboulghar (1999).

THE FIRST CLASSIFICATION OF OHSS

Rabau et al. (1967) proposed the first classification of OHSS which combined both laboratory and clinical findings (Table I.2). The authors reported one of the original series of ovulation induction in 110 patients who had undergone 202 courses of treatment. In most instances, hyperstimulation was limited to increased estrogen and pregnanediol urinary excretion values without palpable cysts or enlargement of the ovaries. In seven cases the authors noted ovarian enlargement or cysts, low abdominal pain and/or distention and nausea (Group 3, Table I.3). Five of the seven patients in Group 3 also vomited or complained of diarrhea (Group 4). The authors classified Groups 3 and 4 as mild adverse reactions. They hospitalized these two groups to prevent exacerbation or further complications (Mozes et al., 1965). In seven patients, the clinical presentation was enlargement of the ovaries, distention, cysts, nausea, and diarrhea and ascites. Four of these seven patients also had hydrothorax (Group 5). Three patients

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Table I.1 Classifications of ovarian hyperstimulation syndrome (1967–1999)
Reproduced with permission from Aboulghar and Mansour (2003). Hum Reprod Update ***9****:275–89*

Study	*Mild*	*Moderate*	*Severe*		
Rabau et al. (1967)	*Grade 1*: estrogen >150 μg/24 h and pregnanediol >10 mg/24 h *Grade 2*: + enlarged ovaries and possibly palpable cysts Grade 1 and 2 were not included under the title of mild OHSS	*Grade 3*: grade 2 + confirmed palpable cysts and distended abdomen *Grade 4*: grade 3 + vomiting and possibly diarrhea	*Grade 5*: grade 4 + ascites and possibly hydrothorax		*Grade 6*: grade 5 + changes in blood volume, viscosity and coagulation time
Schenker and Weinstein (1978)	*Grade 1*: estrogen >150 μg/24 h and pregnanediol >10 mg/24 h *Grade 2*: grade 1 + enlarged ovaries, sometimes small cysts	*Grade 3*: grade 2 + abdominal distension *Grade 4*: grade 3 + nausea, vomiting and/or diarrhea	*Grade 5*: grade 4 + large ovarian cysts, ascites and/or hydrothorax		*Grade 6*: marked hemoconcentration + increased blood viscosity and possibly coagulation abnormalities
Golan et al. (1989)	*Grade 1*: abdominal distension and discomfort *Grade 2*: grade 1 + nausea, vomiting and/or diarrhea, enlarged ovaries 5–12 cm	*Grade 3*: grade 2 + ultrasound evidence of ascites	*Grade 4*: grade 3 + clinical evidence of ascites and/or hydrothorax and breathing difficulties		*Grade 5*: grade 4 + hemoconcentration, increased blood viscosity, coagulation abnormality and diminished renal perfusion
Navot et al. (1992)	–		*Severe OHSS*: variable enlarged ovary: massive ascites ± hydrothorax: hemocrit >45%: WBC >15 000; oliguria: creatinine 1.0–1.5; creatinine clearance ≥50 ml/min; liver dysfunction; anasarca		*Critical OHSS*: variable enlarged ovary: tense ascites ± hydrothorax: hemocrit >55%; WBC >25 000; oliguria: creatinine >1.6; creatinine clearance <50 ml/min; renal failure; thromboembolic phenomena; adult respiratory distress syndrome
Rizk and Aboulghar (1999)	–	Discomfort, pain, nausea, distension, ultrasonic evidence of ascites and enlarged ovaries, normal hematological and biological profiles	*Grade A*: dyspnoea, oliguria, nausea, vomiting, diarrhea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, ultrasound showing large ovaries and marked ascites, normal biochemical profile	*Grade B*: grade A + massive tension ascites, markedly enlarged ovaries, severe dyspnea and marked oliguria, increased hematocrit, elevated serum creatinine and liver dysfunction	*Grade C*: complications as respiratory distress syndrome, renal shut-down or venous thrombosis

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Table I.2 First classification of OHSS
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			Adverse reactions			
	*No reaction**		*Mild***		*Severe†*	
Laboratory and clinical findings	*1*	*2*	*3*	*4*	*5*	*6*
Estrogens >150 μg/24 h	+	+	+	+	+	+
Pregnanediol >10 mg/24 h	+	+	+	+	+	+
Enlarged ovaries		+	+	+	+	+
Palpable cysts		?	+	+	+	+
Distension of abdomen			+	+	+	+
Nausea			+	+	+	+
Vomiting				+	+	+
Diarrhea				?	+	+
Ascites					+	+
Hydrothorax					?	+
Changes in blood volume, viscosity and coagulation time						+

* No treatment required
** Required observation
† Required hospitalization

from Group 5 subsequently showed changes in blood volume, viscosity and hypercoagulability (Group 6). Groups 5 and 6 needed hospitalization and therapeutic control of blood volume viscosity and coagulation time, as well as evacuation of fluid cavities. Rabau et al. (1967) reclassified Groups 5 and 6 as severe adverse reactions and reported the serious complications and management in a much quoted publication (Mozes et al., 1965).

REORGANIZATION OF OHSS CLASSIFICATION

Schenker and Weinstein (1978) reorganized the classification by Rabau et al. (1967) into three main clinical categories and six grades according to the severity of symptoms and signs, and laboratory findings.

(1) **Mild hyperstimulation**
Grade 1, defined by laboratory findings of estrogen levels above 150 μg/24 h and pregnanediol excretion above 10 mg/24 h
Grade 2, in addition, includes enlargement of ovaries; sometimes small cysts are present

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Table I.3 Mild and severe cases of OHSS
Reproduced with permission from Rabau et al. (1967). *Am J Obstet Gynecol* **98**:92–8

	Mild				*Severe*			
Diagnosis	*Case*	*Ampules of Pergonal*	*hCG (IU)*	*Remarks*	*Case*	*Ampules of Pergonal*	*hCG (IU)*	*Remarks*
Primary amenorrhea	Ge. E.20/31 Le. R. 63/108	25 28	25 000 26 000	Pregnancy –	Do. M. 108/199	22	25 000	pregnancy
Secondary amenorrhea	Ge. P. 21/32	55	29 000	–	Ge. P. 21/34	73	15 000	–
Secondary amenorrhea; MAP + secondary amenorrhea and galactorrhea	Sh. M. 72/121	28	29 000	–	Ki. A. 59/149	14	25 000	pregnancy
Postpartum amenorrhea and galactorrhea	Lo. S. 40/67	19	25 000	Pregnancy	Bi. F. 11/17 Ba. A. 13/21	3460	21 500 25 000	quadruplet abortion
Anovulation	Iv. B. 1/1 Hi. E. 89/163	2927	20 000 25 000	–	Be. Z. 19/29	20	10 000	–
Proliferative follicular phase				–	Po. A. 53/90	20	25 000	twin pregnancy

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(2) **Moderate hyperstimulation**
Grade 3, in addition to elevated urinary steroid levels and ovarian cysts, abdominal distension is present
Grade 4, nausea, vomiting and/or diarrhea are also observed

(3) **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

MODERNIZATION OF THE OHSS CLASSIFICATION

Golan et al. (1989) proposed a new classification in which 24-hour urinary assays of hormones became obsolete, and subsequently estrogen and pregnanediol assays were also omitted. Nausea, vomiting and abdominal distension were relocated from moderate to mild OHSS, and then moderate OHSS was no longer divided into two different grades as in the previous specification; it mainly added ultrasound evidence of ascites to the features of Grade 2 OHSS. In my opinion, this was an important addition. Severe OHSS was classified into two grades (Grade 4 and 5), which were similar to the previous classification.

(1) **Mild OHSS**
Grade 1, abdominal distension and discomfort
Grade 2, features of grade 1 plus nausea, vomiting and/or diarrhea; ovaries are enlarged from 5 to 12 cm

(2) **Moderate OHSS**
Grade 3, features of mild OHSS plus ultrasonic evidence of ascites

(3) **Severe OHSS**
Grade 4, features of moderate OHSS plus evidence of ascites and/or hydrothorax and breathing difficulties
Grade 5, all of the above, plus change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormality, and diminished renal perfusion and function

DESIGNATION OF CRITICAL OHSS AS A SPECIAL ENTITY

Navot et al. (1992) suggested making a distinction between severe and life-threatening OHSS by dividing it into two subgroups. Severe OHSS was characterized by variably enlarged ovaries, massive ascites and/or hydrothorax, hematocrit over 45%, WBC $>$ 15 000, oliguria, creatinine of 1.0–1.5 and

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creatinine clearance of ≥50 ml/min. Furthermore, generalized edema and liver dysfunction were considered to be signs of severe OHSS. Critical OHSS was characterized by enlarged ovaries, tense ascites, hematocrit of over 55%, WBC ≥25 000, oliguria, creatinine ≥1.6 and creatinine clearance <50 ml/min. Renal failure, thromboembolic phenomena and adult respiratory distress syndrome (ARDS) constituted critical OHSS. This subdivision was important from both clinical and prognostic aspects. The group of patients labeled as critical OHSS should be treated under very close supervision in an intensive care setting.

CLINICAL CLASSIFICATION OF OHSS

More recently, Rizk and Aboulghar (1999) classified the syndrome into only two categories, moderate and severe. The purpose of this classification is to categorize patients with OHSS into more-defined clinical groups that correlate with the prognosis of the syndrome. This would be ideal from an epidemiological point of view to set a registry for these cases. Furthermore, treatment could be advised depending on which group the patient belongs to.

The mild category of OHSS, as in previous classifications by Rabau et al. (1967) and Golan et al. (1989), was omitted from our new classification, as this occurs in the majority of cases of ovarian stimulation and does not require special treatment. The great majority of cases of OHSS presenting with symptoms belong to the moderate categories of OHSS. In addition to the presence of ascites on ultrasound, the patients' complaints are usually limited to mild abdominal pain and distension, and their hematological and biochemical profiles are normal.

Finally, how does this classification guide treatment of the syndrome? Our new classification can be correlated with the treatment protocol and prognosis more clearly. Severe OHSS Grade C, which is critical, would be treated in an intensive care setting; whereas severe OHSS Grade B would be treated in an inpatient hospital setting with expert supervision. Severe OHSS Grade A could be treated in an inpatient or outpatient setting, depending on the physician's comfort, the patient's compliance and the medical facility. Moderate OHSS could be treated on an outpatient basis with extreme vigilance.

(1) **Moderate OHSS**
Discomfort, pain, nausea, abdominal distension, no clinical evidence of ascites, but ultrasonic evidence of ascites and enlarged ovaries, normal hematological and biological profiles

(2) **Severe OHSS**
Grade A
Dyspnea, oliguria, nausea, vomiting, diarrhea, abdominal pain
Clinical evidence of ascites plus marked distension of abdomen or hydrothorax

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Ultrasound scan showing large ovaries and marked ascites
Normal biochemical profiles

Grade B
All symptoms of grade A, plus:
Massive tension ascites, markedly enlarged ovaries, severe dyspnea and marked oliguria
Biochemical changes in the form of increased hematocrit, elevated serum creatinine and liver dysfunction

Grade C
OHSS complicated by respiratory distress syndrome, renal shut-down or venous thrombosis

EARLY AND LATE OHSS

OHSS in patients undergoing controlled ovarian hyperstimulation has been observed to occur in two distinct forms: early onset and late onset, with possibly different predisposing factors. Early OHSS presents 3 to 7 days after the ovulatory dose of hCG, whereas late OHSS presents 12 to 17 days after hCG. Early OHSS relates to "excessive" preovulatory response to stimulation, whereas late OHSS depends on the occurrence of pregnancy, is more likely to be severe, and is only poorly related to preovulatory events (Dhal-Lyons et al., 1994; Mathur et al., 2000).

SPONTANEOUS AND IATROGENIC OHSS

Traditionally, it has always been stated that OHSS is the most serious iatrogenic complication of ovulation induction. Interestingly, over the last decade, a significant number of reports have been published about spontaneous OHSS without any pharmacological intervention. Most of these cases have been observed in multiple pregnancies (Check et al., 2000) or hyaditiform moles notorious for high hCG values (Ludwig et al., 1998). Some cases were associated with hypothyroidism and the possibility that the high levels of TSH could stimulate the ovaries has been raised (Nappi et al., 1998). A series of cases where recurrent OHSS occurred (Zalel et al., 1995; Olatunbosun et al., 1996; Di Carlo et al., 1997) have been reported. More recently, mutations of FSH receptors have been implicated as a cause for spontaneous OHSS (Vasseur et al., 2003; Smits et al., 2003; Montanelli et al., 2004). Spontaneous forms of OHSS were generally reported to develop between 8 and 14 weeks of amenorrhea. In contrast, iatrogenic OHSS usually starts between 3 and 5 weeks of amenorrhea.

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II

EPIDEMIOLOGY OF OVARIAN HYPERSTIMULATION SYNDROME: IATROGENIC AND SPONTANEOUS

Rizk and Smitz (1992), in an analytical study of the factors that influence the incidence of OHSS, found wide variation between different centers. This is partly because of different definitions for the grades of severity and partly because of the adoption of different criteria for prevention. The incidence of OHSS has been estimated at 20–33% for mild cases, moderate cases of OHSS are estimated at 3–6%, and severe cases at 0.1–2% (Rizk, 1993a, b; Serour et al., 1998, Mathur et al., 2000).

THE IMPACT OF IN VITRO FERTILIZATION ON THE DEVELOPMENT OF OHSS

The development of in vitro fertilization (IVF) by Professor Robert Edwards and Dr. Patrick Steptoe was the gateway to modern human reproduction (Steptoe and Edwards, 1978). The impact of IVF on reproductive medicine has been phenomenal. It opened new horizons in every discipline from cell biology to genetics. Robert Edwards is a legend of the twentieth century, and it is always fascinating to see that he had already thought of and debated issues in the 1960s and 1970s that our profession and society are just discovering (Aboulghar et al. 1998a). In relation to ovarian stimulation, Louise Brown was conceived after natural-cycle IVF without gonadotrophins. The use of gonadotrophins became popular in the early 1980s. It is interesting to note that the incidence of OHSS following IVF in the 1980s (Table II.1) was higher than that following ovulation induction in the 1970s without the widespread use of estradiol monitoring or ultrasonography (Table II.2).

Rizk and Smitz (1992) thought this high incidence possibly represents an increase in aggressiveness in stimulation during the 1980s, and secondarily the use of long GnRH agonist protocols. Professor Edwards was among the first *to question the wisdom of aggressive ovarian stimulation* and advocated a gentle approach (Edwards et al., 1996; Fauser et al., 1999). The best example of this very serious epidemic has been clearly demonstrated by Abramov et al. (1999). In a multicenter report of OHSS cases from 16 out of 19 tertiary medical centers in Israel, the authors revealed some shocking findings. While the number of severe cases of OHSS following ovulation induction treatments remained unchanged, the number of cases following IVF increased dramatically from 2 (0.06% of all IVF cases in 1987) to 41 (0.24% of all IVF cases in 1996)(Figures II.1 and II.2). The total number of IVF cycles performed during

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