Hepatic Dysfunction Associated with Moderate Ovarian Hyperstimulation Syndrome

A Case Report

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BACKGROUND: Liver dysfunction is a rare complication of severe ovarian hyperstimulation syndrome (OHSS). Based on a MEDLINE search from 1966 to September 2000, we report the second case of liver dysfunction associated with moderate OHSS. In addition, this is the first report of moderate OHSS with serum progesterone levels during the first trimester of pregnancy higher than the upper limit of normal for a third-trimester gestation.

CASE: A 33-year-old nulligravida with a history of infertility had previously undergone three failed cycles of assisted reproduction. During her fourth attempt at in vitro *fertilization and intracytoplasmic sperm injection, she developed moderate OHSS 11 days after embryo transfer. She was managed on an outpatient basis. Her serum progesterone and liver enzyme levels were significantly elevated, as is unusual for the moderate picture of OHSS in this patient.*

CONCLUSION: Hepatic dysfunction is not limited to the severe forms of OHSS. Liver function should be analyzed even in moderate cases. Further study is needed to understand the role of elevated liver function tests and serum progesterone in the pathogenesis of OHSS. (J Reprod Med 2001;46:765–768)

Hepatic dysfunction is not limited to the severe forms of OHSS and may be more common than previously thought.

Keywords: ovarian hyperstimulation syndrome; liver; reproductive techniques; infertility, male.

Introduction

Sueldo et al[1] and Younis et al[2] were the first to report liver dysfunction in severe ovarian hyperstimulation syndrome (OHSS). Since then, abnormal hepatic function has been increasingly recognized as a complication of severe OHSS. Abnormal liver function tests (LFT) were recorded in 37.5% of patients with severe OHSS in a European series.[3] Although abnormal liver function has been reported as a complication of only severe OHSS, elevated LFT in a pa-

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tient with moderate OHSS was reported recently.[4]

After performing a MEDLINE search from 1966 to September 2000 using the key words *OHSS, hyperstimulation syndrome, liver dysfunction, hepatic dysfunction* and progesterone, here we report the second case of moderate OHSS accompanied by liver dysfunction.[4] In our case, there were significant elevations of LFT, which are unusual even in severe cases of OHSS. Based on our review of reported cases of OHSS, we also report the first case of moderate OHSS with a serum progesterone level higher than the upper limit of normal for the third trimester of pregnancy (normal, 48.0–423.0 ng/mL).

Liver function tests should be ordered even in moderate cases.

Case Report

A 33-year-old, obese nulligravida (body mass index 33 kg/m^2) with a history of infertility due to a severe male factor (azospermia) secondary to partial congenital absence of the vas deferens had previously undergone three failed cycles of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) using her husband's spermatozoa surgically retrieved by microsurgical epididymal sperm aspiration (MESA) (Table I). This cycle was her fourth attempt at IVF-ICSI. In all three prior cycles, the patient received luteal-phase GnRHa for down-regulation and then stimulation with hMG and FSH. These cycles are summarized in Table I. In the fourth cycle, after pituitary down-regulation with 1.0 mg subcutaneous leuprolide acetate (Lupron, TAP Pharmaceuticals, Deerfield, Illinois) daily, the patient was started on 3 ampules of rFSH (75 IU/ampule, Follistim, Organon, West Orange, New Jersey) and 1 ampule of hMG (75 IU FSH+75 IU LH/ampule, Repronex, Ferring Pharmaceuticals, Tarrytown, New York). The Lupron was stopped when gonadotropin stimulation commenced. After 12 days of ovarian stimulation requiring a total dose of 44 ampules (32 ampules of rFSH and 12 of hMG), the patient developed eight follicles ranging in diameter from 17 to 21 mm. Her peak estradiol level at the time of hCG injection was 3,114 pg/mL.

Ultrasound-guided transvaginal follicular aspiration was performed 35 hours after administration of 10,000 IU hCG (Profasi, Serono Laboratories,

Table I *Characteristics of the Patient's IVF-ICSI Cycles*

Cycle no.	Stimulation protocol	No. of days in stimulation	Total gonadotropin dose (ampules)	E_2 on day of hCG (pg/mL)	No. of follicles (>16 mm) on day of hCG	hCG dose (IU)	No. of oocytes retrieved	No. of embryos transferred	Luteal support protocol	Progesterone on 10th–14th day after transfer (ng/mL)
1	GnRHa/FSH/hCG	11	39	3,077	10	5,000	19	5	Progesterone in oil, 50 mg bid	n/a
2	GnRHa/FSH/hCG	13	48	5,669	7	5,000	13	4	Progesterone in oil, 50 mg bid	n/a
3	GnRHa/FSH+hMG/hCG	13	58 (37 FSH+21 hMG)	4,773	8	5,000	22	4	Progesterone in oil, 50 mg bid	38
4	stopGnRHa/FSH+hMG/hCG[a]	12	44 (32 FSH+12 hMG)	3,114	8	10,000	19	6	Progesterone in oil, 50 mg bid, + hCG 1,500 IU every 3 days	576

[a]GnRHa was stopped at the follicular phase.
n/a = Not available.

Table II *The Patient's Laboratory Results*

Day after transfer	Hemoglobin (g/dL)	Hematocrit (%)	WBCs ($10^3/mm^3$)	Protein (g/dL)	Albumin (g/dL)	AST (IU/L)	ALT (IU/L)	hCG (IU/L)	Progesterone (mg/mL)
11	15.1	46.2	16.5	6.0	3.2	71	90	n/a	n/a
13	14.0	45.4	15.6	5.8	3.1	150	168	409	576
15	12.8	38.4	11.3	6.5	3.5	456	265	778	509
16	12.3	36.9	10.4	n/a	n/a	74	156	n/a	n/a
20	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5,645	570
34	n/a	n/a	n/a	n/a	n/a	n/a	n/a	136,622	363
60	12.2	36.6	10.0	6.5	3.3	26	17	n/a	151

n/a = Not available.

Norwell, Massachusetts), and 19 oocytes were retrieved. Frozen sperm obtained from a MESA procedure were utilized. Utilizing ICSI, 13 oocytes were fertilized. After an extensive discussion with the patient, who had undergone three previous failed attempts with four to five embryos transferred, a decision was made to transfer six embryos into the uterine cavity three days after retrieval. Luteal support consisted of a combination of hCG, 1,500 IU every three days, and progesterone in oil, 50 mg intramuscularly twice daily.

On the 11th day after embryo transfer, the patient complained of abdominal distention, bloating and itching. Her blood pressure was 105/70 mm Hg and pulse rate, 76 bpm. The patient had gained 4.1 kg over the previous 14 days. Her abdomen was moderately distended, yet she had no evidence of abdominal pain or respiratory compromise. Transvaginal ultrasonography showed both ovaries to be multicystic and enlarged to 6–8 cm and confirmed the presence of ascites. Table II summarizes the laboratory results. There was no history of previous liver disease. Normal results were obtained for total bilirubin, LDH and alkaline phosphatase. Serologic tests for viral hepatitis were normal. Progesterone and booster hCG injections were discontinued. The patient was given instructions about the danger signals for OHSS and was seen frequently on an outpatient basis for moderate OHSS. Bed rest and an abundant fluid intake were advised. Fluid retention was monitored by daily body weight and abdominal girth measurements.

During follow-up, serum progesterone levels peaked at 576 ng/mL. Serum progesterone was determined by using a direct chemiluminescent immunoassay (Chiron Diagnostics Corporation, East Walpole, Massachusetts). The intraassay and interassay coefficients of variation were <10%. Because the values were high, samples were diluted 1:10 and run in duplicate. The dilution recoveries of the assay kit were between 98% and 118%. The serum AST and ALT levels peaked at 456 IU/L (normal, 10.0–40.0) and 265 IU/L (normal, 10.0–50.0), respectively. Other LFT remained in the normal range. Abdominal ultrasound showed a normal liver and gallbladder. Ascites and ovarian sizes did not change until post-ET day 18. Thereafter, the patient's symptomatology improved, ascites began to gradually decrease, and enlargement of ovaries began to regress.

On post-ET day 20, ultrasound showed three gestational sacs in the uterine cavity. At this writing the patient was in her second trimester of a triplet gestation.

Discussion

This is the second report of moderate OHSS and liver dysfunction.[4] Several classifications have been proposed for OHSS. The often-used classification by Golan et al[5] is composed of five grades. Our patient fit Golan's moderate OHSS picture (grade 3) and was managed on an outpatient basis.

Triplet gestation and OHSS were potentially preventable in this case. However, when the patient's prolonged infertility history, three previous failed cycles and peak estradiol level were considered, the decision to transfer six embryos was made. Our protocol for luteal phase support in IVF includes either hCG or progesterone. However, in this patient, after discussing her three previous failed cycles and the risk of early pregnancy loss due to her obesity, both luteal hCG and progesterone were given to support the luteal phase.[6] The luteal hCG may have contributed to the development of OHSS.

In this case the serum AST and ALT levels peaked to 456 and 256 IU, respectively, which is higher than the levels reported by Wakim et al[4] and rare even in cases of severe OHSS.[7] Serum AST

and ALT levels in patients with severe OHSS are usually <200 IU/L.[4,7] We considered hepatitis part of the differential diagnosis. However, viral titers were all normal. The hepatic dysfunction in this case may have been due to the hCG, progesterone in oil or OHSS. Miura et al[8] reported hepatic dysfunction during pregnancy due to haptenic sensitization to endogenous hCG.[8] Although our patient conceived in an IVF-ICSI cycle, her symptoms quickly improved despite progressively rising hCG levels.

The cause of elevated LFT in OHSS remains unclear. The proposed mechanisms are increased circulating sex steroid concentrations, chemical hepatitis, hepatocellular damage from the increased vascular permeability that characterizes severe OHSS and hepatic ischemia/reperfusion as a result of circulatory dysfunction in severe OHSS.[7]

In our case the serum progesterone level peaked at 576 ng/mL. This level is above the upper normal level for the third trimester of pregnancy for our laboratory (normal, 48.0–423.0). To our knowledge, this case is the first reported one of moderate OHSS with a high serum progesterone level (>423.0 ng/mL). High levels of progesterone have previously been reported in two cases of severe OHSS.[9,10] The significance of progesterone in the pathogenesis of OHSS is unclear. Animal studies have shown that progesterone increases capillary permeability and causes ovarian enlargement.[11] The two mechanisms that have been reported for these effects of progesterone are increased VEGF production and activation of the ovarian kinin-kallikrein system.[12,13] Both effects induce increased capillary permeability.[12,13]

Recently Chen et al reported that abnormal LFT in patients with OHSS was associated with lower clinical pregnancy rates.[7] However, all the patients had severe OHSS. Based on our review of the literature and our own report, moderate OHSS cases associated with hepatic dysfunction are not always associated with poor pregnancy outcomes.[4] However, further studies with larger groups of patients are necessary to understand the significance of elevated LFT in both moderate and severe OHSS.

In conclusion, hepatic dysfunction is not limited to the severe forms of OHSS and may be more common than previously thought. This suggests that liver function tests should be ordered even in moderate cases. Further study is needed to understand the role of elevated LFT and serum progesterone in the pathogenesis of OHSS.

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