SEVERE OVARIAN HYPERSTIMULATION SYNDROME: REPORT OF 3 CASES AND LITERATURE REVIEW

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Abstract We presented three cases of severe ovarian hyperstimulation syndrome that occurred amongst 59 infertility women who underwent ovarian superovulation with gonadotropin releasing-hormone agonist (GnRH, Buserelin, Hoechst) plus human menopausal gonadotropin (hMG, Pergonal, Serono) and human chorionic gonadotropin (hCG, Profasi, Serono) in assisted reproductive programme. Hospitalization was required for severe symptoms. Every case had ascitic fluid more than 1,000 ml with abdominal distention. One of them had respiratory discomfort due to ascites and hydrothorax. Hypoproteinemia was also noted in these patients but no hemoconcentration or thromboembolism was detected. Multiple abdominal paracentesis were done to relieve the symptom, two cases conceived but one aborted at 14 weeks and the other went to term unevenfully.

Literature review for identifying patient at risk, pathogenesis, preventive measures and therapeutic approaches were described. Chiang Mai Med Bull 1992; 31:205-212.

Introduction

Induction of ovulation is an important step for assisted reproductive procedure in the treatment of infertility. Many agents were introduced into this field e.g. clomiphene citrate, human menopausal gonadotropin (hMG), follicular stimulating hormone (FSH), gonadotropin releasing hormone agonist (GnRHa) and combination of these drugs. However, they have not only benefit in producing many oocytes but can also be harmful to the patient. Ovarian
hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovulation induction. Despite less common occurring nowadays, it still has a very serious impact on the health and may cause severe morbidity, even mortality to the patient. We now present three cases of OHSS.

Patient 1

A Thai-female patient, 34 years of age, has 3-year duration of primary infertility with uneventful medical history. Infertility work-up revealed normal male partner but laparoscopic examination detected minimal endometriosis with patent both tubes. Clomiphene citrate was prescribed and she conceived later. Miscarriage was encountered at 14 weeks of gestation. Ovulation induction with GnRHα/hMG/hCG was tried after failure of clomiphene citrate. She conceived again. Unfortunately, she had spontaneous abortion at 11 weeks. Superovulation along with timing intercourse was used but failure to conceive in more than one year period. Gamete intrafallopian transfer (GIFT) was introduced. Ovarian superovulation with long protocol was prescribed. Before hCG injection, serum E2 was 4,100 pg/ml and ultrasonogram demonstrated 5 cm in diameter of both ovaries containing plenty of follicles larger than 10 mm in diameter. GIFT was performed by minilaparotomy and hCG was used for luteal support. Postoperative period, she had abdominal distention (abdominal girth 87 cm) and respiratory discomfort due to marked ascites and mild to moderate hydrothorax. Ovarian enlargement 5.8 x 6.4 cm and 5.6 x 6.3 cm in diameter were shown by ultrasound. Hypoproteinemia was demonstrated (4.4 gm%) No hematologic abnormality was found. Liver and kidney function were normal. Biochemical pregnancy was diagnosed and ultrasound later showed a single viable fetus in utero. During 7 weeks period of hospitalization, supportive treatment was given to alleviate the symptom. Six abdominal paracentesis were done under ultrasound guidance (1,500-3,000 ml in 1-2 hours) and replaced 20% human albumin to maintain oncotic pressure. At 12 weeks gestation, vaginal bleeding was encountered and pregnancy ended at 14 weeks spontaneously. Karyotype of the conceptus was not done but those of the parents were normal.

Patient 2

A 36-year-old woman had 5 year period of infertility. She had subtotal hemithyroidectomy due to single unilateral nodular thyroid goiter 10 years ago. No other medical problem was noted. The male partner had oligoasthenospermia. Pelvic examination revealed a left mobile 5-cm adnexal cyst. Laparoscopic examination revealed 5-cm left hydatid cyst of Morgagni and bilateral cornual-obstruction. Excision of the cyst and cornual
implantation were performed. She conceived one year later but unfortunately spontaneous miscarriage was encountered and no more pregnancy occurred during the two following years. Repeat laparoscopic examination demonstrated peritubal adhesion and bilateral tubal occlusion at cornue. Despite reexploratory laparotomy for adhesiolysis and bilateral tubal implantation at posterior wall of the uterus, tubal obstruction was documented again a year later. IVF was scheduled by ovarian superovulation with GnRHα/hMG/hCG in long protocol. The E2 level before hCG injection was 2,000 pg/ml. Both ovaries were 4 x 4.5 cm and 4.2 x 4.4 cm in diameter, containing 11 follicles larger than 10 mm in diameter. Transvaginal oocyte retrieval was done and obtained 8 oocytes. Four embryos were transferred into uterine cavity and supported luteal phase with hCG. Six days later, she had nausea and marked abdominal distention (abdominal girth 84 cm) but no pleural effusion. No hemoconcentration was detected. Kidney and liver function were normal except mild hypoproteinemia (5.0 gm%). Ultrasound showed ovarian enlargement measuring 5.4 x 6.3 cm and 5.5 x 6.5 cm in left and right side respectively. Pregnancy was diagnosed by means of serum B-hCG assay and ultrasound. Her pregnancy went on well. Ascites regressed spontaneously in 2 weeks. She spent 6 days in the hospital. At 39 gestational weeks, she delivered a male fetus weighing 3,600 gm by cesarean section.

**Patient 3**

A 36-year old patient had 5 years duration of infertility. She had no obvious medical problem except dysmenorrhea. Her couple was normal on infertility work-up. Laparoscopic examination disclosed severe endometriosis (score 74) with tubal obstruction. Exploratory laparotomy to lysis adhesion and fimbrioplasty was performed but she failed to conceive due to recurrent tubal obstruction. IVF was offered and ovarian stimulation was done with GnRHα/hMG/hCG in long protocol. The E2 level before hCG injection was 3,650 pg/ml and ultrasonogram of both ovaries were 3.3 x 5.0 cm and 3.4 x 5.2 cm in diameter which contained more than 15 follicles which were bigger than 10 mm in diameter. Eighteen oocytes were collected under vaginal ultrasound guidance. Embryo transfer was done within 48 hours. hCG was used for luteal support. Nine days later, she developed abdominal distention due to ascitic fluid collection (abdominal girth 83 cm). Ultrasonogram demonstrated enlargement of both ovaries measuring 3 x 5.5 cm and 3.4 x 5.9 cm in right and left side. No hemoconcentration was found. Kidney function was normal. Mild hypoproteinemia (5.0 gm%) was detected. She had been hospitalized for 4 days. Ascites was reabsorbed spontaneously within 1 week. No pregnancy occurred.
Discussion

Ovarian hyperstimulation syndrome (OHSS) is a serious complication of ovulation induction. It occurred 5-10 days after hCG injection. Schenker and Weinstein summarized the incidence of mild OHSS was 8-23 %, moderate 0.005-7 % and severe 0.008-10 % (less than 2 % in most series). (1) The patient at risk to develop OHSS is polycystic ovarian disease (PCOD), Group II ovulatory disorder, (2) young age, (3) lean body, (3) pregnant cycle, (4) preovulatory follicle (9-15 mm) more than five, (5) rapid increasing of E2 level (4) or serum E2 more than 2,000 pg/ml associated with a total more than 15 follicles each bigger than 12 mm mean diameter (6) and bilateral ovarian enlargement over 6 cm. (7)

Rabau et al classified OHSS in three main clinical categories and six grades then modified by Schenker and Weinstein which based on clinical presentation and laboratory findings. But recently, Golán et al. proposed new classification system as follows. (8)

Mild OHSS

Grade 1. Abdominal distention and discomfort.

Grade 2. Features of grade 1 plus nausea, vomiting, and/or diarrhea. Ovaries are enlarge to 5 to 12 cm.

Moderate OHSS

Grade 3. Features of mild OHSS plus ultrasonic evidence of ascites.

Severe OHSS

Grade 4. Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax or breathing difficulties.

Grade 5. All of the above plus change in blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function.

Our patients were classified as grade 4 of severe OHSS because they had clinical evidence of ascites and/or hydrothorax or dyspnea.

Pathogenesis of OHSS is composed of two components. Firstly, ovarian enlargement caused by multiple ovarian cyst formation with stromal edema. Secondary, acute fluid shifts out of the intravascular space which may result in ascites, hydrothorax and even generalized edema. The fluid shift is caused by an increase of the capillary permeability of ovarian vein, peritoneum, omentum and pleura (9, 10) which allow fluid escape into the third space and may lead to hypovolemia, hyperviscosity, hypercoagulability, oliguria, renal failure, electrolyte disturbances (11) and impaired liver function (12). Many substances had been postulated to increase vascular permeability e.g. estrogen, progesterone, testosterone, proactin, histamine, ovarian prorenin and prostaglandin (8, 11, 13, 14).
If pregnancy does not occur, the ovarian enlargement gradually declines until the menstrual flow starts. If conception occurs, further ovarian enlargement generally follows late in the cycle because of additional hCG stimulation following implantation. The condition can progress to a severe form.\(^{(15)}\)

Mild OHSS does not require any active therapy other than observation and rest. Moderate OHSS should be admitted to the hospital.\(^{(8)}\) Severe OHSS needs hospitalization and prompt treatment. The patient should be carefully examined and the basic investigation such as complete blood cell count, electrolytes, renal function tests, liver function tests, blood and urine osmolarity and clotting factors should be made. The circulatory condition should be assessed and central venous pressure recorded in more severe patients. The ovaries should be screened by ultrasonography and accurately measured, and the presence of pleural effusion and ascites noted. Vaginal examination should be avoided, as the risk of rupturing an ovarian cyst outweighs its merits. Colloidal plasma expanders, such as dextran or albumin, can be given to maintain colloid pressure and replace protein losses.\(^{(6)}\) Fluid balance is very important and urinary output must be carefully monitored. Salt and water restriction are not advocated. In addition, diuretics can induce hypovolemia, so it is prohibited.\(^{(7)}\)

Indomethacin (a prostaglandin synthetase inhibitor), chlorpheniramine maleate and cyproheptadine (antihistamine) have been used to modify the symptoms of OHSS. GnRH agonist and danazol, both known to interfere with ovulation and ovarian steroidogenesis, may help to suppress OHSS.\(^{(6,7)}\) Anticoagulant therapy is needed only when evidence of thromboembolism appears.

Surgery is indicated only in the presence of torsion or rupture of an ovarian cyst\(^{(15)}\) and should be performed by an experienced gynecologist.\(^{(7)}\) Abdominal paracentesis has been suggested as a palliative measure to alleviate the discomfort associated with tense ascites and respiratory distress.\(^{(16)}\) The procedure must be carried out under ultrasonographic control to avoid puncture of an enlarged ovarian cyst transabdominally or transvaginally.\(^{(17)}\)

The incidence of OHSS can be reduced by monitoring serum estradiol levels along with measuring follicular growth with ultrasonic equipment.\(^{(6,15)}\) The administration of hCG is critical for the development or prevention of OHSS. If the patient is high risk for developing OHSS, hCG should be withheld and GnRH is continued until the menstrual flow starts.\(^{(15)}\) The new cycle can be commenced by lowering the hMG dosage than initially used when serum E\(_2\) levels was below 20 pg/ml and no follicles more than 3 mm were presented in either ovary. If hCG was given, oocyte retrieval
must be performed thoroughly (18) and gametes or embryo transfer should be delayed to the next cycle. Cryopreservation of the embryos was recommended (19). If OHSS, however, was developed and luteal support considered necessary, it would be prudent to use progesterone rather than hCG (6, 20).

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กลุ่มอาการร่างไข่ถูกกระตุ้นมากเกินไปอย่างรุนแรง:
รายงานผู้ป่วย 3 ราย และบททวนเอกสาร

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บทคัดย่อ รายงานนี้เป็นการรายงานผู้ป่วย 3 รายที่เกิดอาการร่างไข่ถูกกระตุ้นมากเกินไปอย่างรุนแรงจากคำว่าผู้ป่วยที่มี
บุตรชาย 69 ราย ซึ่งได้รับการกระตุ้นการกระตุ้นด้วย GnRHa กับ hMG และ hCG เพื่อรักษาภาวะมรณะ
หน้าที่บุตรโดยการรักษาด้วยโครงย้าย โดยมีอาการต่อจากระหว่างน้ำในช่องท้องมากกว่า 1 สิ่ง มีปัญหาในหน้าที่ช่อง
สุร่าย 1 ราย มีอาการหายใจลำบากที่น้ำในช่องท้องและช่องบุตรและได้รับการรักษาโดยการเจาะน้ำในช่องท้องโดยกล้า
ครั้ง มีผู้ป่วยติดต่อ 2 ราย แต่ห่างจากอายุการตั้งครรภ์ 14 สิ่งครา 1 ราย และอีก 1 ราย ติดต่อก่อต่อไปจนครบกำหนด  นอกจากนี้
ยังได้บททวนเอกสารเกี่ยวกับกลุ่มอาการที่ใช้เพื่อเป็นแนวทางในการจุดรักษาต่อไป เชิงทางวิทยาศาสตร์ 2535;31:205-212.