

Spontaneous Pregnancy with Severe Ovarian Hyperstimulation Syndrome Undergoing IVF-ET Cycle: A Case Report and Review

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Short communication

Keywords: In vitro fertilization and embryo transfer, Ovarian hyperstimulation syndrome, Spontaneous pregnancy, Controlled ovarian hyperstimulation, Polycystic ovary syndrome

Posted Date: December 10th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-122462/v1>

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Abstract

It is relatively rare that a natural spontaneous with severe ovarian hyperstimulation syndrome (OHSS) occurs undergoing in vitro fertilization and embryo transfer (IVF-ET). Pregnancy can cause OHSS to be delayed, and even lead to pregnancy loss in severe cases. In this case, we introduced the case of a 32-year-old female infertile patient with PCOS who underwent IVF-ET cycle and developed severe OHSS before embryo transfer. After volume expansion, symptomatic and supportive treatment and four times of abdominal puncture to extract ascites, the patient's condition is still protracted. However, interestingly, two weeks after giving up treatment, the patient found a spontaneous pregnancy and ended up with biochemical pregnancy. Severe OHSS was also gradually self-healing after biochemical pregnancy. This case emphasizes that pregnancy is one of the high-risk factors of OHSS, which can lead to the delay of the patient's condition with OHSS. Clinicians should be alert to the possibility of spontaneous pregnancy when they take luteal phase ovulation induction treatment undergoing IVF-ET cycle.

Synopsis

Ovarian hyperstimulation syndrome (ovarian hyperstimulation syndrome, OHSS) mainly occurs in the treatment of assisted reproductive technology (ART), when the ovaries are over-stimulated by ovulation drugs [1–2]. With the increasing maturity of ART in the treatment of infertility, the widespread application of COH has led to the incidence of OHSS as high as 8.14%~23.3%, and increasing year by year [3]. At present, the pathogenesis of OHSS is not completely clear, and its clinical symptoms vary from severity to severity, often accompanied by pleural effusion, ascites, electrolyte disorders, oliguria and liver and kidney damage [4–5]. At present, there is no specific treatment plan for OHSS, but if it can be detected early, given timely expansion, and symptomatic supportive treatment, good therapeutic effects can be achieved. However, most of the OHSS cases described in the above report occurred during COH treatment cycle, after oocyte retrieval, and occurred at 3 to 5 weeks of pregnancy after fresh embryo transfer [6]. However, it is rarely reported that cases of spontaneous pregnancy combined with severe OHSS occurred during COH treatment cycle. Here, we describe the case of a 32-year-old infertile woman with PCOS who became pregnant naturally during luteal phase ovulation induction treatment cycle and developed persistent severe OHSS after oocyte retrieval. After discharge from the hospital, the patient was found to be pregnant during the follow-up visit, and the condition was self-healing after biochemical pregnancy. This situation should be highly valued and correctly prevented and treated.

Case Introduction

A 32-year-old female was admitted to the reproductive center of Taiyuan Central Hospital for "three years of marriage, without contraception and pregnancy for one year after biochemical pregnancy". Combined with clinical symptoms and auxiliary examination, the preliminary diagnosis is primary infertility, PCOS and ovulatory dysfunction. The proposed therapeutic schedule was Letrozole for ovulation induction, and follicular development was monitored by vaginal type B ultrasound until ovulation to guide the coitus behavior on proper time. Letrozole 50 mg was given on the fifth day of menstruation, once a day for

5 days. Vaginal type B ultrasound monitoring on the 10th day of menstruation showed that multiple follicles were developing at the same time, but there was no dominant follicle. At the same time, we checked estradiol (E2) 89.87 ng/L and progesterone(P) 0.86 ng/mL. therefore, the treatment plan was changed to IVF-ET and luteal phase stimulate ovulation. On the 10th day of menstruation, 150 IU of gonadotropin (Gn) was given. On the 6th day of Gn intervention, vaginal type B ultrasound was used to monitor the slow growth of follicles, and then the dosage was increased to 225 IU. On the 13th day of Gn intervention, vaginal type B ultrasound monitoring of follicles revealed 13 follicles with a diameter of ≥ 1.6 cm. E2 1 485.24 ng/L, luteinizing hormone (LH) 1.75 mIU/mL, and P 47.5 ng/mL were checked. Ovulation was triggered by intramuscular injection of 10 000 IU of chorionic gonadotropin(hCG) at 21:30 on the same day. Thirty-six hours later, puncture follicles retrieval were performed under the guidance of vaginal type B ultrasound. Operation procedure: The patient took the bladder lithotomy position, and routinely disinfected the vulva and vagina. The vaginal type B ultrasound showed clear sound images of the bilateral ovaries. 11 follicles were observed and 4 oocytes were obtained. The operation process went smoothly.

4 days after the follicles retrieval, the patient had slight abdominal distension, no nausea, vomiting and other adverse reactions. The vaginal type B ultrasound monitoring showed that the right ovary was 13.2 cm \times 8.2 cm, and multiple anechoic areas were found in the right ovary, the larger one was 4.5 cm in diameter, and the left ovary was 13.0 cm \times 10.0 cm in diameter. The larger one was 5.0 cm, and the irregular liquid dark area was about 7.3 cm in abdominal cavity and 13.7 cm in pelvic cavity. Considering the patient's medical history, physical signs and auxiliary examination, the patient was considered as moderate OHSS. Therefore, fresh embryo transfer was cancelled and all embryos were frozen. It was recommended that the patient be hospitalized, but the patient refused to be hospitalized.

Eight days after the follicles retrieval, the patient complained of obvious abdominal distension, accompanied by nausea, no vomiting, no sense of suppression in the chest and other symptoms, and the abdominal percussion was suspected to be positive. Reexamination of vaginal type B ultrasound showed that the right ovary was 17.5 cm \times 7.8 cm, and there were multiple anechoic lesions in the right ovary. The diameter of the larger ovary was 4.3 \times 2.7 cm, and the left ovary was 16.3 cm \times 9.4 cm. The diameter of the larger ovary was 3.4 \times 4.7 cm. The irregular liquid dark area in the pelvic cavity was about 5.6 cm, and the liver kidney space was deep about 8.8 cm. Combined with symptoms, signs and auxiliary examination, the diagnosis was severe OHSS. Combined with the patient's symptoms, signs and auxiliary examinations, it was diagnosed as severe OHSS. Considering that the patient's condition was serious, he was admitted to the hospital and received symptomatic treatment such as hydroxyethyl starch 1300 0.4 sodium chloride injection and albumin volume expansion. After admission, the relevant examination was improved. After the patient signed the informed consent form, transvaginal posterior fornix aspiration was performed under sterile conditions. After 13 days of volume expansion, symptomatic supportive treatment and four times of abdominal puncture and drainage treatment, the condition continued to recur. At this time, the patient refused to continue treatment and asked to be discharged. The relevant biochemical indexes and vaginal type B ultrasound examination results of the patients during the treatment are shown in Fig. 1, Table1 and Table2.

Table 1
biochemical indexes

Biochemical indexes Time	8th day after oocyte retrieval	11th day after oocyte retrieval	13th day after oocyte retrieval	16th day after oocyte retrieval	20th day after oocyte retrieval
TP(normal, 65–85 g/L)	39	39	37.5	39.9	42.2
ALB(normal,40–55 g/L)	24.2	24	23.7	23.8	26.8
GLB(normal,20–40 g/L)	14.8	16	13.8	16.1	15.4
FIB(normal, 2–4 g/L)	5.81	5.11	5.56	5.56	5.33
D- D(normal, 0–0.55 mg/mL)	5.5	5.2	5	3.8	3.7
WBC(normal,3.5–9.5 10^9 /L)	15.92	14.61	12.72	12.4	11.1
RBC(normal,4.3–5.8 10^{12} /L)	4.65	4.28	4.29	4.09	3.43
HGB(normal,130–175 g/L)	143	133	127	127	102
PLT(normal,125–350 10^9 /L)	592	606	647	663	642
Volume of ascites extracted (ml)	2000	3300	3380	-	3595
24-hour intake(ml)	2452	3380	2430	3504	3650
24-hour output(ml)	3720	2090	2170	2890	3290
TP: Total protein; ALB:Albumin; GLB:Globulin ; FIB:Fibrinogen ;D-D:D-Dimer ; WBC: white blood cell; RBC: Red blood cell; HGB:Hemoglobin; PLT:Platelet					

Table 2
the results of vaginal type B ultrasound monitoring

Vaginal type B ultrasound Time	3th day of menstruation	4th day after oocyte retrieval	8th day after oocyte retrieval	11th day after oocyte retrieval	13th day after oocyte retrieval
Left ovary(cm)	2.6 × 1.5	13.0 × 10.0	16.3 × 9.4	13.0 × 10.0	12.0 × 7.8
Right ovary(cm)	2.9 × 1.3	13.2 × 8.2	17.5 × 7.8	15.0 × 11.0	11.7 × 6.2
Ascites(cm)	-	7.3	8.8	8.6	9.5
Pelvic effusion(cm)	2.6	13.7	5.6	16.8	11.8

After discharge, the patient was asked to review regularly. 31 days after oocyte retrieval, the patient's menstruation was delayed for 2 weeks. The urine pregnancy test was positive, and the serum hCG was 527 mIU / ml; 32 days after oocyte retrieval, the serum HCG was reexamined at 500 mIU / ml; The serum HCG was 404 mIU / ml at 35 days after oocyte retrieval; Blood HCG was 267 mIU / ml at 39 days after oocyte retrieval, considering biochemical pregnancy, OHSS gradually healed.

Discussion

The overall incidence rate of OHSS was 3.1%~8.0% in IVF-ET cycle, and the incidence rate of high-risk patients could be as high as 20%[7]. According to the World Health Organization(WHO), the incidence of moderate OHSS is 3 ~ 6%, and the incidence of severe OHSS is 0.1 ~ 2%[8].

The pathogenesis of OHSS is not fully understood, which may be related to the production of various vasoactive substances in the ovaries stimulated by HCG[9–10]. The increase of hCG level in OHSS patients triggers the mutation of FSH receptor, which leads to the increase of corresponding downstream hormones[11]. In addition, hCG is highly sensitive to mutant FSH receptor (FSHR) and glycoprotein hormones with the same subunits are over secreted[12]. However, pregnancy patients themselves also produce more endogenous HCG, which may also be another possible mechanism of OHSS. Recent studies have also shown that all FSHR gene activation mutations are associated with OHSS[13–14].

The main pathological changes of OHSS were multiple follicles and multiple corpus luteum cysts with interstitial edema, which caused ovarian enlargement and abnormal volume[15]. In addition, increased capillary permeability causes fluid to flow into the extravascular cavity, leading to pleural effusion, ascites, pericardial effusion, and even systemic edema. These changes can lead to hypovolemia and the increase of blood drug concentration, which can easily lead to the formation of intravascular thrombosis, renal perfusion insufficiency, and then oliguria and electrolyte disorder[16–17].

The key to prevent OHSS is early identification of high-risk factors, including youth, low body mass index, polycystic ovary syndrome, hypothyroidism, rapid increase of serum E2 levels and previous history of OHSS[18–20]. We should pay attention to the clinical intervention before the treatment of COH cycle in high-risk groups. During ovulation induction, we should closely monitor blood E2 and B-ultrasound, monitor the size and quantity of follicles. The stimulation program and the dosage of Gn should be adjusted in time to prevent the occurrence of OHSS. Mild OHSS is mostly self-healing. The main purpose of moderate and severe OHSS treatment is capacity expansion and symptomatic and supportive treatment. Early and timely give human serum albumin, low molecular dextran and other intravenous drip to correct blood volume and improve microcirculation[21]. For patients with a large amount of hydrothorax and ascites with chest tightness and abdominal distension pain, it is the quickest and most effective treatment method to improve symptoms. For severe OHSS with more follicles, puncture and aspiration of follicles can achieve good results.

In this case, the risk factors of OHSS included age < 35 years old, polycystic ovary syndrome, hCG triggering ovulation and pregnancy. Age < 35 years old is an independent risk factor for OHSS. There are

more antral follicles in the ovaries of young patients, and the number of follicles collected during COH cycle is also increased. In addition, there are a large number of Gn receptors in the ovaries of young patients, and they are prone to overreaction to Gn. PCOS is an ovulation disorder and endocrine disease, which affects about 26% of women of childbearing age[22]. It significantly increases the risk of OHSS during COH cycle[23]. The gonadotropin required for follicular development is quite different during COH cycle, and the follicular development is difficult to control. HCG is widely used in ART cycles for COH cycle and luteal support. Exogenous hCG can increase the content of the internal hCG, activate renin angiotensin system, and enhance the activities of renin, angiotensin and their invertase, thus producing angiotensin II, the ultimate active substance, resulting in the increase of vascular permeability and the occurrence of OHSS.

In this case, the patient developed moderate OHSS 4 days after oocyte retrieval, and was not hospitalized in time. 8 days after oocyte retrieval, the patient developed into severe OHSS and was hospitalized. After 13 days of volume expansion, supportive symptomatic treatment and four times of peritoneal puncture fluid extraction treatment, the patient's condition was still delayed. Finally, the patient was discharged because she refused to continue treatment. Two weeks after discharge, urine HCG was tested positive and blood HCG gradually decreased, and biochemical pregnancy was considered. The patient did not undergo fresh embryo transplantation due to the consideration of moderate OHSS 4 days after oocyte retrieval. Then, when was the embryo implanted?

After make a detailed inquiry of the patient's medical history, we learned that the patient had no history of coitus during the luteal phase ovulation induction period, but had a history of coitus during letrozole ovulation induction period. Therefore, it was inferred that the patient had ovulation during letrozole ovulation induction period, and normal fertilization and implantation occurred. It is considered that the placenta trophoblast secretes a large amount of endogenous hCG due to pregnancy, which increases the risk of severe OHSS and prolongs the course of disease. Other studies have found that hCG plays a key role in promoting the release of VEGF, which can increase the activity of VEGF[24], thus aggravating the patient's condition.

Conclusion

Age < 35 years old, PCOS, hCG triggered ovulation and pregnancy were the high risk factors of OHSS during COH cycle. Before the treatment of COH, the patients should be evaluated comprehensively and individualized. At the same time, attention should be paid to early identification of high-risk factors of OHSS. It is worth noting that pregnancy is not only a high-risk factor of OHSS, but also can aggravate the progress of OHSS, leading to repeated and prolonged disease. Some scholars believe that the outcome of pregnancy after severe OHSS is similar to that of pregnancy undergoing IVF cycle, so special care is not needed[25]. However, it has been reported that the intelligence of offspring of OHSS patients is decreased, and prenatal estradiol exposure may be related to its pathogenesis[26]. In conclusion, more attention should be paid to monitoring the occurrence of pregnancy during COH cycle, especially for those who adopt the luteal ovulation induction program, those patients with OHSS who are not cured after

hospitalization and active expansion and symptomatic supportive treatment should be alert to the possibility of pregnancy, and those with severe symptoms should consider timely termination of pregnancy.

Abbreviations

OHSS: ovarian hyperstimulation syndrome;

PCOS: polycystic ovary syndrome;

IVF-ET: in vitro fertilization and embryo transfer;

COH: controlled ovarian hyperstimulation;

ART:assisted reproductive technology;

hCG: chorionic gonadotropin;

VEGF: vascular endothelial growth factor;

E2:estradiol ;

P: progesterone;

LH:luteinizing hormone;

Gn:gonadotropin

Declarations

Acknowledgments

None.

Funding

None.

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Contributions

Study design: Peng CN and Wang ZX. Study implementation: Peng CN. Data collection: Peng CN and Wang ZX. Drafting of the manuscript: Peng CN. Approval of final version of the manuscript: Wang ZX. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

All authors have confirmed that this work complies with the International Committee of Medical Journal Editors (ICMJE) and the Declaration of Helsinki.

Consent for publication

Written informed consents for this publication were previously obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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Figures

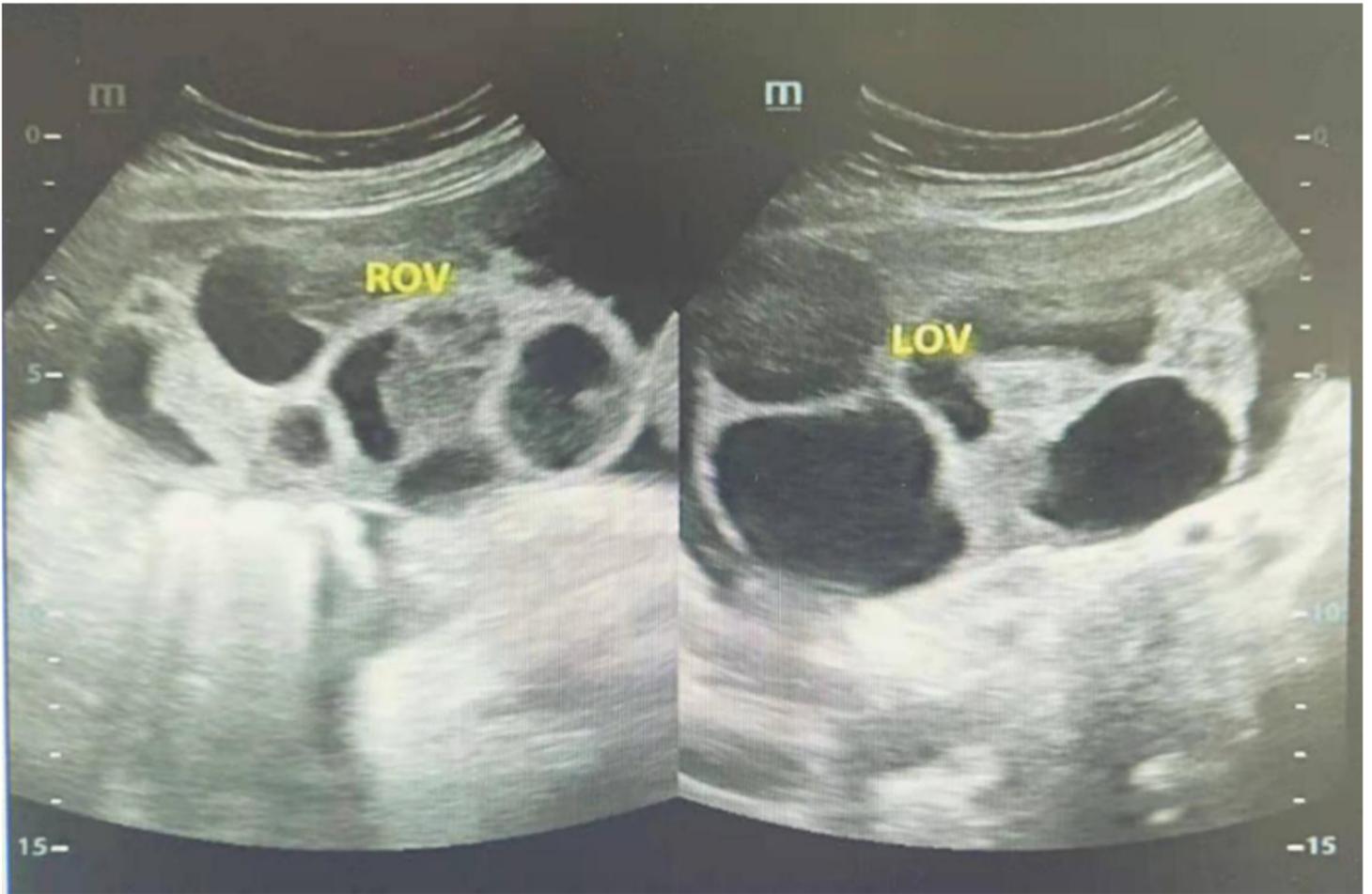


Figure 1

the results of vaginal type B ultrasound monitoring on the 8th day after oocyte retrieval