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Ectopic pregnancy and failed oocyte retrieval during *in vitro* fertilization stimulation: Two case reports

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Abstract

BACKGROUND

Due to a slight rise in beta-human chorionic (β -hCG) levels that are undetectable, and vaginal bleeding that is similar to regular menstruation, ectopic pregnancy (EP) that occurs during the expected menstrual cycle prior to ovulation induction as part of *in vitro* fertilization (IVF) is likely to be undiagnosed. We present two cases of unexpected EP and emphasize the importance of the β -hCG assay when an unexplained increase in progesterone is present prior to the triggering of ovulation during controlled ovarian stimulation (COS).

CASE SUMMARY

A 26-year-old woman with primary infertility and a 31-year-old woman with secondary infertility. Both patients sought IVF treatment due to fallopian tube obstruction and underwent COS using the gonadotropin-releasing-hormone (GnRH)-antagonist protocol. In the late stage of COS, progesterone levels in both patients significantly increased, and luteinizing hormone levels decreased, followed by oocyte retrieval failure. A right salpingectomy was performed and tubal ectopic pregnancy was diagnosed by pathology in the first patient, and the second patients was diagnosed with a suspected EP abortion because her β -hCG levels declined to 12.5 mIU/mL. After full recovery for 2 mo, the first patient entered a new IVF treatment cycle with a GnRH-antagonist regimen and successfully achieved eight oocytes and three viable embryos. After 6 mo, the second patient received another COS treatment with a progestin-primed ovarian stimulation protocol and successfully achieved nine oocytes and five viable embryos.

CONCLUSION

β -hCG levels in the initial and midterm phases of COS must be considered in patients with unusual hormone dynamics.

Key Words: Infertility; Ectopic pregnancy; *In vitro* fertilization; Ovarian induction; Case

report

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Core Tip: In this report, we present two cases of undiagnosed ectopic pregnancies during controlled ovulation stimulation (COS) who sought *in vitro* fertilization treatment due to fallopian tube obstruction. In the late stage of COS, progesterone levels in both patients significantly increased and luteinizing hormone (LH) levels decreased, followed by oocyte retrieval failure. These cases emphasized the importance of vigilance about patients with unexplained increases in progesterone and decreases in LH during the COS process. Further, the examination of human chorionic gonadotropin in the initial and midterm phases of COS should be considered essential for patients with unusual hormone dynamics.

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INTRODUCTION

The incidence of ectopic pregnancy (EP) in patients undergoing *in vitro* fertilization (IVF) is 1.5%-2.1% [1], which is higher than that in natural conception. The epidemiology and risk factors of EP after IVF have been widely investigated. Several hypotheses have been proposed to explain this difference, including high proportion of abnormal tubal function, hormonal environments, technical aspects of IVF procedures, and estimated embryo implantation potential [2]. Usually, doctors have high vigilance for EP after embryo transfer and most EPs can be diagnosed early by measuring beta-human chorionic gonadotropin (β -hCG) serum levels and through transvaginal ultrasound. However, the occurrence of EP during the controlled ovarian stimulation (COS) process is rarely reported. As almost one third of women with EP have no clinical signs and 9% have no symptoms, the early diagnosing of EP with β -hCG is important for clinicians, especially before the start of ovary stimulation. While, it was reported that about 1% of EPs will have a negative urine pregnancy test and a β -hCG level of less than 20 mIU/mL [3]. Herein, we present two cases of unexpected EP with initial very low serum β -hCG levels during COS and emphasize the importance of the β -hCG assay when an unexplained increase in progesterone is present prior to the triggering of ovulation during COS.

CASE PRESENTATION

Chief complaints

The basic characteristics of the two patients in COS cycle are displayed in Table 1 and the serial sex hormone levels and follicle sizes of the two patients during COS are shown in Figure 1. Both received IVF treatment because of fallopian tube factors, and neither had a history of EP.

Case 1: The patient was 26-year-old, gestation 0 parturition 0. She had a medical history of bilateral fallopian tube proximal obstruction diagnosed by hysterosalpingogram (HSG).

Case 2: The patient 2, 30-year-old and gestation 2 parturition 0, had already had one previous IVF cycle in other clinic (five oocytes retrieval and one embryo transfer, no pregnant).

History of present illness

Case 1: From 18th March, follicle stimulating hormone (FSH) (Gonal-F, Merck Serono, Darmstadt, Germany) was administered at 200 IU/d for 6 d. The dose was adjusted to 150 IU/d for another 5 d according to the ovarian response. A gonadotropin release hormone (GnRH)-antagonist (0.25 mg) (Cetrotide, Merck Serono, Darmstadt, Germany) was administered beginning on day 7 of stimulation and was combined with menotropin (75 IU) for injection (HMG, LIVZON Inc., China). On March 28th, hCG (7000 IU) (HCG; LIVZON Inc., China) was injected to trigger ovulation. Thirty six hours later, the presence of all the follicles were confirmed by transvaginal ultrasonography (TVS) before the performance of oocyte aspiration. No oocyte was retrieved despite the repeatedly flushing of all the follicles. We noticed the follicular fluid being deep yellow which suggested oocyte premature luteinized. On that day, the serum β -hCG, estrogen and progesterone serum concentrations measured

Table 1 Basal characteristics of the two patients

	Case 1	Case 2
Age (yr)	26	30
Indication for IVF	Bilateral fallopian tube obstruction	Right uterus cornual obstruction and partially obstruction of left fallopian tube
Primary/secondary infertility	Primary	Secondary
Hormone levels on day 2 nd of COS cycle		
FSH (mIU/ml)	8.92	8.16
LH (mIU/ml)	1.37	4.95
E2 (pg/ml)	33	23
P (ng/ml)	0.39	0.75
β-hCG (mIU/ml)	2.77	2.36
AMH (ng/ml)	1.3	2.6
COS description		
Total quantity of Gn	2325 IU	2100 IU
Duration of COS	10 d	13 d
Numbers of retrieved oocytes	0	0

IVF: *In vitro* fertilization; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; β-hCG: Beta human chorionic gonadotropin; AMH: Anti-Müllerian hormone; IU: International units; Gn: Gonadotropin; COS: Controlled ovarian stimulation.

just after the failed oocyte retrieval were 7401 mIU/mL, 2607 pg/mL and 14.21 ng/mL, respectively.

Case 2: Because of right uterus cornual obstruction and partially obstruction of left fallopian tube diagnosed by HSG she did not become pregnant. From the 14th of October, menotropin (300 IU) (HMG; LIVZON Inc., China) was injected per day for 12 d. GnRH-antagonist (0.25 mg) (Cetrotide; Merck Serono, Darmstadt, Germany) was started on day 9 and continued to the trigger day. The patient was given hCG (7000 IU) (HCG; LIVZON Inc., China) intramuscularly on October 27th to trigger ovulation. After 36 h, no sign of ovulation was observed through TVS before oocyte retrieval but no oocytes were retrieved despite repeated flushing.

Personal and family history

Case 1: She had reported a regular menstrual cycle (4-5 d/30-31 d) and the last menstrual period (LMP) was on March 17th 2020 with normal vaginal bleeding. She declared the previous menstrual period as February 20th 2020 and an unprotected sexual behavior on March 9th. Her husband's sperm test was normal (concentration of 65.1×10^6 /mL and a + b = 23.3% + 25.2%).

Case 2: She had a regular menstrual cycle (4-5 d/28 d) with LMP reported as October 13th 2020 and normal vaginal bleeding as usual.

Physical examination

Normal vaginal bleeding as usual menstruation and negative abdominal pain.

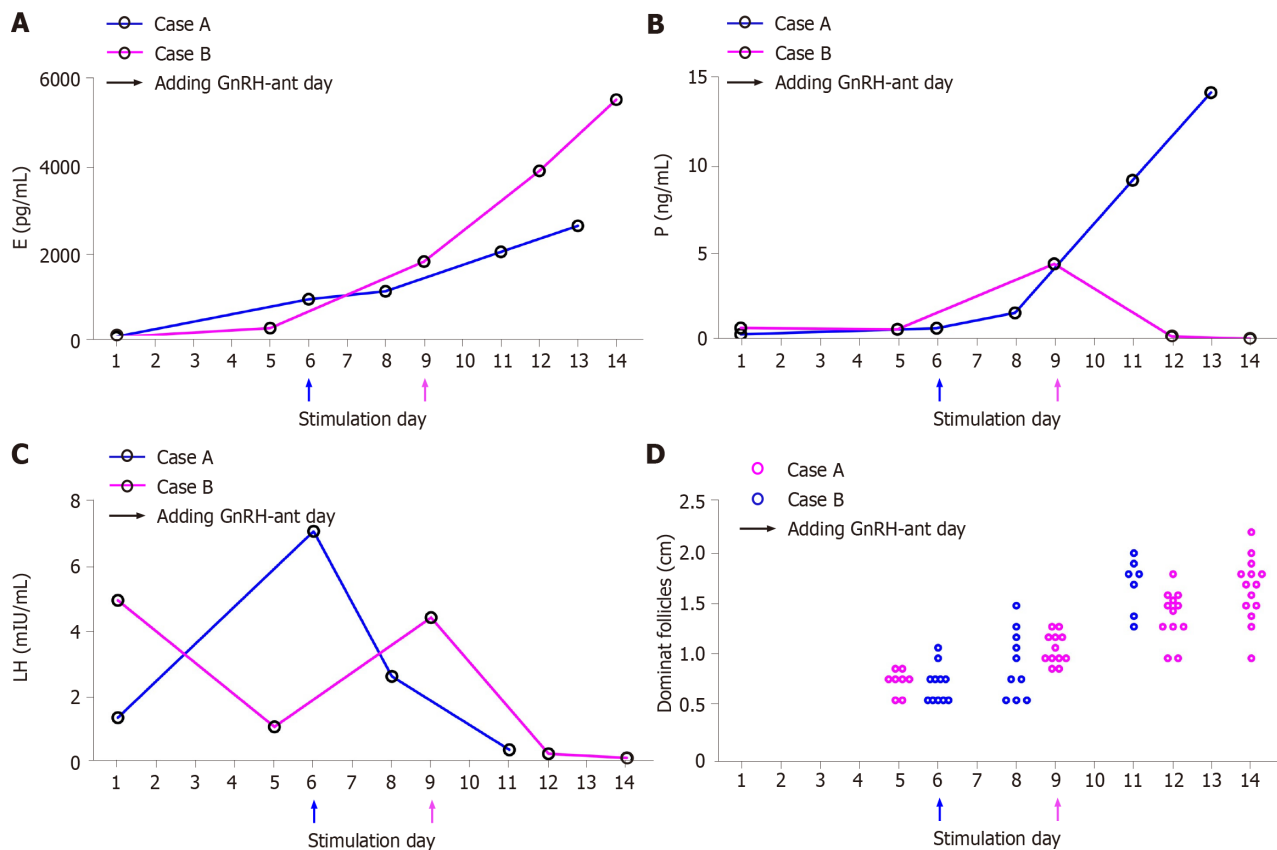
Laboratory examinations

Case 1: The day following oocyte retrieval, TVS indicated a pseudogestational sac in the right adnexa (16 mm × 14 mm × 12 mm), with an increased β-hCG level measuring 8432 mIU/mL.

Case 2: Her β-hCG level had declined 3 d later after the intervention to 327.8 mIU/mL. Five days later, her β-hCG level had further declined to 12.5 mIU/mL.

FINAL DIAGNOSIS

Case 1: Laparoscopy was performed right now. Intraoperative findings proved right fallopian tube ectopic pregnancy as well as approximately 500 cc of clotted fresh blood in the pelvis. Finally, tubal ectopic pregnancy was diagnosed by pathology.



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Figure 1 Sex hormones level and dominant follicle diameter of two patients during ovulation induction. A: Luteinizing hormone; B: Estradiol; C: Progesterone; D: Dominant follicle diameter. GnRH-ant: Gonadotropin-releasing-hormone-antagonist.

Case 2: The serum β -hCG levels in patient 2 increased from 366.08 mIU/mL on oocyte retrieval day to 592 and 1286.7 mIU/mL on day 7 and 15 following oocyte retrieval, respectively. TVS performed 15 d following oocyte retrieval indicated that no pregnancy sac in the uterus and a suspicious mass (5 mm \times 8 mm \times 9 mm) located in the right adnexa. Three days later, the patient experienced vaginal bleeding and her serum β -hCG levels declined. Therefore, a suspected EP abortion was considered for patient 2.

TREATMENT

Case 1: Right salpingectomy was performed.

Case 2: The blood values and ultrasound of the patients were followed up, and no other special treatment was given.

OUTCOME AND FOLLOW-UP

Case 1: After full recovery for 2 mo, the patient entered a new IVF treatment cycle with GnRH-antagonist regimen and successfully achieved eight oocytes and three viable embryos.

Case 2: After 6 mo, the patients received another COS treatment with a progestin-primed ovarian stimulation protocol and successfully achieved nine oocytes and five viable embryos.

DISCUSSION

Oocyte retrieval failure is an adverse outcome of IVF cycles, and early luteinization is one of the major reasons. However, to the best of our knowledge, oocyte retrieval failure caused by accidental EP during ovulation has not yet been reported.

The exclusion of pregnancy before ovary stimulation is necessary, either with the administration of oral or injection medicines. Usually, urine pregnancy test is affordable and convenient. However, EP before ovary stimulation might be misdiagnosed due to low β -hCG levels in early pregnancy. In a normal intrauterine pregnancy, β -hCG can be detected in the plasma as early as eight days after ovulation[4] and will reach 50-300 mIU/mL within two weeks of fertilization[5]. It has been shown that about 85% of women with EP display lower β -hCG levels than those in normal pregnancies, and one retrospective study of 207 patients with EP reported that 2.6% of EPs had a low serum β -hCG level of under 20 mIU/mL and more than 1% of EPs have been reported to have undetectable levels of β -hCG[6, 7].

Not all patients with EP displayed a classic triad of symptoms, including delayed menses, vaginal bleeding, and lower abdominal pain. Simultaneous measurement of serum estradiol (E2) and progesterone levels is helpful for the early diagnosis of EP when there are undetectable serum β -hCG levels. Usually, estradiol levels > 100 pg/mL or progesterone levels > 3 ng/mL after 14 d of ovulation suggest sustained endogenous luteal activity[8]. However, the present two cases displayed normal estradiol and progesterone levels on the second day of the menstrual cycle, with β -hCG measuring 2.77 mIU/mL and 2.36 mIU/mL, respectively. Also, neither patient declared any of the typical EP symptoms throughout the COS procedure, resulting in failure to diagnose EP before oocyte retrieval.

During the COS procedures in these cases, both patients showed normal elevated estrogen concentration and follicle size, indicating that the follicles could develop under the stimulation of exogenous FSH, even during pregnancy. However, luteinizing hormone (LH) levels dropped and progesterone levels increased dramatically in the late COS phase. Follicular development during pregnancy is unusual because the low levels of circulating gonadotropins suppressed by high inhibin and P levels. However, the exogenous administration of gonadotropins can overcome this inhibition and induce follicular development[9-11]. A case of follicular growth in response to clomiphene citrate (CC) has been reported in the presence of an EP by Bayrak *et al*[12]. They observed multiple follicular development in a woman receiving superovulation with CC in spite of the presence of an undiagnosed ovarian EP. And more interestingly, follicular growth even occurred in the ovary which the EP was eventually diagnosed in. The women did not receive trigger medicine before intrauterine insemination as the ovulation kit was positive and no ovulation was confirmed by ultrasound. In 2017, Orvieto *et al*[13] reported a case of ovarian hyperstimulation syndrome (OHSS) following GnRH agonist trigger and freeze-all, masking EP. The 36 years old woman displayed normal estradiol (146 pmol/L) and progesterone (0.8 nmol/L) level on day 3. During 8 d of ovary stimulating, her E2 and P levels continued to rise and reached a peak E2 level of 14533 pmol/L and P level of 12.8 nmol/L. She was triggered with GnRH agonist 0.3 mg, yielding 6 matured oocytes that were vitrified. Six days following ovum pick up, the woman was admitted to ward with typical OHSS signs and her serum β -hCG revealed of 2881 IU/L. The patient was diagnosed as right tubal EP through TVS and offered intramuscular methotrexate injection right now. Goeckenjan *et al*[14] also demonstrated the feasibility of triggering final follicular maturation by GnRH- antagonist after stimulating and recruiting ovarian follicles during pregnancy. However, the effect of gonadotrophin administration on the development of EP was still not reported.

Because of the homology between hCG and LH, hCG can be used as a surrogate for the LH surge [15]. In COH with antagonist protocol, both hCG and GnRH agonist, which evoke endogenous LH surge, could be used as trigger. Compared with LH, hCG has a longer half-life and may exert a more lasting effect on LH receptors[16]. In cases presented here, we failed to yield oocytes by triggering with hCG, which was different from the previously reported cases. What's more, the character of follicular fluid indicated premature luteinization of follicles. Reviewing the reports by Orvieto *et al*[13] and Goeckenjan *et al*[14], the level of β -hCG of patients during late follicle phase was lower than those in our report. Therefore, it is questionable which factor resulted in the failure of oocyte retrieval, trigger medicine or premature luteinization induced by higher β -hCG?

Until now, the effect of high β -hCG on oocyte quality was absent. Several studies have reported that co-treatment with low dose hCG (200 IU/d) before or in the early stage of COS may enhance developmental competence of oocytes and provide an effective way to reduce rFSH use[16,17]. Other studies have also demonstrated that the addition of low-dose hCG (50-200 IU/d) in the late follicular stage during ovarian stimulation can effectively promote follicular development and maturation and improve implantation and ongoing pregnancy rates[18,19]. However, it should be noted the probability of premature luteinization of granulosa cells induced by a significant increase in β -hCG at the late follicular stage.

CONCLUSION

In conclusion, our cases illustrate the ongoing clinical diagnostic challenges associated with EP that occurs during COS, which is rare. When an unexplained increase in progesterone levels occurs during ovulation induction, apart from considering the early onset of LH surge, testing for serum β -hCG to exclude pregnancy is recommended, especially to rule out the potentially life-threatening diagnosis of EP. Whenever the pregnancy is proven, oocyte retrieval should be cancelled and the risk of OHSS be

cautioned.

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