SHORT COMMUNICATION

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An Unusual Case of Rebound Ovulation During Conservative Management of an Ectopic Pregnancy Following Ovum Donation

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INTRODUCTION

Increasingly, nonsurgical management of ectopic pregnancy is being advocated as the treatment of choice in properly selected patients (1). At most 5–10% of selected cases fail treatment and require surgical intervention. However, many failures are secondary to pain intolerance, leading to physician intervention for fear of tubal rupture. We present an ectopic pregnancy in a recipient of a donated ovum who was successfully treated using methotrexate. Her difficult and unusual clinical course illustrates the challenges of medical management of ectopic pregnancy and the importance of understanding the patient's underlying reproductive status where the expected hormonal changes of a gravid patient cannot necessarily be assumed.

CASE REPORT

The patient, a 43-year-old gravida 1 para 0010, had a 3-year history of secondary infertility. She previously underwent a right salpingostomy for an ectopic pregnancy, at which time dense adhesions and uterine leiomyomata were described. Subsequently, a hysterosalpingogram revealed a right hydrosalpinx, left tubal spill, and a normal uterine cavity. She next attempted but failed two cycles of in vitro fertilization and

embryo transfer. The patient was later referred for ovum donation.

The evaluation prior to oocyte donation demonstrated the patient's hysterosalpingogram to be unchanged. Other examinations including a semen analysis, chest X-ray, ECG, pap smear, and mammogram were unremarkable. Her medical history was significant for frequent constipation requiring laxative use.

The patient was matched and synchronized using Lupron suppression, which was discontinued on day 9 of her oral estrace and im progesterone (P) regimen to an oocyte donor who provided 12 oocytes, of which 7 fertilized. Four four-cell preembryos transferred transcervically without difficulty. The uterus was previously sounded to 8.5 cm and the embryo transfer was accomplished using a Tomcat catheter. The patient was sent home on micronized estradiol (4 mg daily) and intramuscular P (100 mg daily).

She returned 12 days posttransfer for pregnancy testing, at which time the serum β -human chorionic gonadotropin β -hCG was found to be 23 mIU/ml (second IS), rising to 405 mIU/ml 1 week later. Levels continued to rise appropriately and the patient was asymptomatic.

Four weeks posttransfer, a transvaginal ultrasound (USG) examination visualized a single ectopic gestation (CRL, 5.3 mm at 5 weeks $\pm$ 6 days) located in the right adnexae. Doppler flow studies, which have been described previously for the monitoring of ectopic pregnancy (2), demonstrated both systolic and diastolic flow. The patient was stable hemodynamically, with a hematocrit of 40%. She was given the option of surgical or medical management, and chose combined par-enteral and intratubal methotrexate therapy.

Salpingocentesis was performed using direct embryonic injection of 2 ml of 50 mg of methotrexate was performed under ultrasound guidance (day 0 treatment). Cardiac motion was observed to cease. No bleeding was seen after 15 min of observation. Examination performed 3 hr later depicted no further changes. An intramuscular injection of methotrexate (50 mg)

was given to the patient prior to discharge and all hormonal supplementation was discontinued. The β -hCG level was 13,767 mIU/ml.

The patient was monitored daily by telephone contact and frequent office visits. She returned on day +2 and day +4 from initial treatment, and as expected, β -hCG values were noted to be increased to 16,849 and 24,242 mIU/ml. During that time her serum P declined but remained elevated (18.8 to 6.7 ng/ml). A USG showed a 2.3×1.8 -cm dilated tube but no cul-de-sac fluid. However, because Doppler studies of the ectopic continued to show both systolic and diastolic flow, a second injection of methotrexate 50 mg was given intramuscularly. On day +6, the serum β -hCG fell 29%, to 17,134 mIU/ml and the Hct remained stable (37%). However, because serum P remained elevated at 5.1 ng/ml and Doppler revealed persistent flow, a third injection of methotrexate (50 mg) was given. From day +6 to day +11, the β -hCG dropped 37.6%, to 10,678 mIU/ml, and the serum P decreased to 1.5 ng/ml. The USG remained unchanged except for loss of systolic and diastolic-flow to the ectopic gestation.

The night of day +11, the patient presented to the ER with sudden onset of lower abdominal pain and weakness. USG revealed 40 ml of cul-de-sac fluid, and a decrease in size of the ectopic. No systolic and diastolic blood flow was again noted and it was felt that a tubal abortion had occurred. The hemotocrit was 30.4%, with normal PT/PTT and electrolytes. Bimanual pelvic examination was deferred to avoid tubal rupture. The patient was observed and given a laxative to facilitate a bowel movement. She felt better immediately and was discharged home.

On day +15, hCG and serum P were 4385 mIU/ml and 1.1 ng/ml. USG showed the hydrosalpinx to be unchanged, however, the left ovary now revealed three cystic structures measuring $5.0 \times 4.6 \times 4.0$ cm in total. The largest cyst was 2.4 cm in diameter, with increased systolic and diastolic flow compared to the right ovary. The ovary appeared similar to that of a patient undergoing ovarian hyperstimulation (Fig. 1).

On day +18, the patient felt improved and her levels continued to decline (1197 mIU/ml). However, the serum P increased to 3.5 ng/ml. The USG and Doppler flow studies remained unchanged, although the ovarian cysts had the appearance of newly formed corpus lutea, consistent with ovulation. That afternoon, the patient had another episode of acute-onset abdominal pain, again relieved with a bowel movement.

The patient remained symptom free and β -hCG levels continued to decline (day, +21, 536 mIU/ml; day

+27, 166 mIU/ml; day +35, 16 mIU/ml; day +42, <5 mIU/ml). Serum P increased from 2.9 ng/ml on day +21 to 11 ng/ml on day +27. Approximately 14 days after the appearance of the ovarian cysts, P fell to <1.0 ng/ml, however, the USG continued to show the dilated tube, which remained unchanged, and the three ovarian cysts, which eventually resolved by day +72.

DISCUSSION

The management of ectopic pregnancy has changed dramatically over the past two decades. Methotrexate, a folate antagonist, has been used successfully in increasing numbers of cases. Modifications in its administration has occurred since first reported in 1981. Direct salpingocentesis has also been advocated instead of intramuscular administration (3).

Medical management of ectopic pregnancy remains clinically challenging, especially in cases with well-developed tubal pregnancies (cardiac activity). Even in experienced hands, failure rates approach 15%. Complete resolution is prolonged and leads to physician and patient frustration. Compliance often becomes problematic, as careful surveillance and repeated dosing are necessary.

This case illustrates several interesting and novel aspects. Ectopic pregnancy in women undergoing ovum donation is uncommon, occurring in <1% of established pregnancies. Similar to other clinical situations resulting in ectopic pregnancies, conservative management with parenteral and direct intratubal injection and diagnostic tools including Doppler flow studies is appropriate in well-selected patients. However, following the withdrawal of hormonal supplementation, a "rebound" ovulation may occur. This results from the withdrawal of suppressive exogenous steroids, leading to a burst of endogenous gonadotropins which stimulate the development of new follicles. "Rebound" ovulation and pregnancy have been reported previously in patients on hormone replacement for premature ovarian failure (4). Thus, in our patient, despite the declining serum β -hCG, the appearance of multiple follicular cysts and the dramatic rise in serum P are consistent with ovulation. This complicated the clinical picture. The sudden onset of pain on day +11 to day +18 may have reflected "Mittelschmerz." This could mislead caretaking physicians to conclude that the treatment had failed, resulting in surgery. Serial ultrasounds with Doppler flow studies, limiting the number of pelvic examinations which confirmed

Fig. 1. USG on day +15.

a lack of status change, all resulted in a correct interpretation of the clinical picture.

Pregnancies have been reported following discontinuation of hormonal replacement in patients with presumed ovarian failure, therefore, patients with ectopics undergoing methotrexate treatment should either continue their hormone replacement or be placed on oral contraceptives to prevent potential ovulation. Although extremely unlikely, a subsequent rise in serum β -hCG would have been interpreted a treatment failure, rather than a spontaneous conception following "rebound" ovulation.

SUMMARY

Conservative medical management of ectopic gestations may be difficult in patients with elevated levels of β -hCG and cardiac activity. This case highlights the difficulty of managing such patients. Doppler flow studies and serum P, if available, should be used and can help determine those patients requiring repeated dosing of methotrexate. Patients using donor gametes and hormonal supplementation who subsequently develop an ectopic gestation may experience "rebound" ovulation, which further clouds the clinical picture. Careful follow-up using serial blood testing and ultrasound study is essential in the correct interpretation of a potentially confusing clinical picture.

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