Clomiphene citrate-induced follicular development in the presence of an ovarian ectopic pregnancy

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Objective: To describe a case of a patient who had multiple follicular growth in the presence of an undiagnosed ectopic pregnancy (EP).
Design: Case report.
Setting: In vitro fertilization unit at a university hospital.
Patient(s): A 34-year-old patient with secondary infertility.
Intervention(s): Superovulation with clomiphene citrate (CC) and IUI.
Main Outcome Measure(s): Follicular development with CC stimulation documented by transvaginal ultrasound and β-hCG levels.
Result(s): Two co-dominant follicles were observed with mean diameters of 22 mm and 24 mm. The patient had unexpectedly high levels of β-hCG at the time of missed menses and was subsequently diagnosed with an ovarian EP.
Conclusion(s): Multiple follicular growths can occur in response to CC in spite of the presence of an ovarian EP. (Fertil Steril® 2008;89:456.e1–2. ©2008 by American Society for Reproductive Medicine.)

Key Words: Clomiphene citrate, ectopic pregnancy, follicle growth, ovarian ectopic

Follicular development and ovulation during pregnancy is an uncommon phenomenon in humans because of suppressed gonadotropins at the pituitary gland (1). However, exogenous administration of gonadotropins can overcome this phenomenon and induce follicular development (2–4). Even in the presence of low gonadotropins and low GnRH levels in pregnancy, follicular development in response to clomiphene citrate (CC) has been reported to occur (5). We present a case of CC-induced follicle development in the presence of an ovarian ectopic pregnancy (EP).

CASE REPORT

A 34-year-old nulliparous patient presented with secondary infertility for 3 years. She denied any significant medical, surgical, or gynecological history and reported regular monthly menses every 28 days with a documented midluteal serum P level of 20 ng/mL. The husband had a normal semen analysis. The patient had previously undergone a diagnostic hysteroscopy for the evaluation of the endometrial cavity, which was reported as being normal. She gave a history of CC and gonadotropin use for two cycles 3 months before presenting to our center.

Received July 11, 2006; revised March 5, 2007; accepted March 13, 2007.
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After extensive discussion of treatment options, the couple decided to undergo superovulation with CC and IUI. On cycle day 3, the transvaginal sonogram (TVS) examination was normal. Hormone analyses of FSH and E_2 revealed serum levels of 8.0 mIU/mL and 76 pg/mL, respectively. The patient was then administered CC at a dose of 100 mg orally for 5 days. The patient returned on day 15 of her cycle for evaluation and stated that the ovulation kit might have been faintly positive two nights before. A TVS examination revealed fluid in the cul-de-sac and two small antral follicles in each ovary. The couple had intercourse on days 12 and 14 of the cycle. It was assumed that the patient had already ovulated and insemination was withheld. Patient returned to clinic 18 days after her last visit on the third day of her "menses."

The patient had a normal TVS examination and hormone analysis for FSH and E_2, which were 10.7 mIU/mL and 59 pg/mL. Patient desired to start another CC and insemination cycle, and was given the same dose of medicine and instructed to return to the clinic on day 10 for closer monitoring during this cycle. On the 10th day of the cycle, two follicles measuring 18 mm each were noted on TVS. The patient notified the office later that same day that the ovulation kit was positive, and was instructed to come in the next day for insemination. Two follicles measuring 22 mm and 24 mm were noted and the patient underwent an IUI that day, which was repeated 24 hours later.

0015-0282/08/$34.00

doi:10.1016/j.fertnstert.2007.03.038

Two weeks later, a serum β-hCG assessment revealed a level of 10,249 mIU/mL, and on repeat analysis it was 10,564 mIU/mL. She denied any symptoms at this time such as abdominal pain or vaginal bleeding. Four days later, the β-hCG level was 13,653 mIU/mL. The TVS revealed a left adnexal mass measuring 3.1 by 3.0 cm in size without any free fluid. The serum from the third day of her previous cycle was reanalyzed for β-hCG and returned 11.4 mIU/mL.

After extensive discussion of the unusual clinical scenario and findings, the patient was taken to the operating room with informed consent with a preoperative diagnosis of EP. Diagnostic laparoscopy revealed a normal uterus and normal bilateral fallopian tubes with bilateral patency on chromopertubation. A left ovarian cystic mass measuring 3 by 3 cm in size was noted. Because of the possibility of ovarian ectopic gestation, an exploratory laparotomy was performed. At laparotomy, a 3- by 3-cm intraovarian mass with a 2-mm rupture site on the left ovary was noted and the mass was resected without any difficulty.

Permanent sections confirmed the attachment of ectopic gestation to the ovarian stroma. Diagnosis of an ovarian EP, defined initially by Spiegelberg (6), was fulfilled by the following criteria: The fallopian tubes on both sides were morphologically normal, patent on chromopertubation, free of any masses or ectopic gestation, gestational sac occupied the normal position of the ovary, gestational sac was connected to the uterus by the ovarian ligament, and on permanent histologic sections ovarian tissue was found in the ectopic gestational sac. A pathologist was called in to the operating room to observe these findings with the surgical team. The postoperative course was unremarkable.

DISCUSSION

Follicular growth during pregnancy is an unusual phenomenon, but has been reported after the administration of exogenous gonadotropins by several investigators (3, 4). Pregnancy is believed to be a period in which no follicular development and ovulation could occur. This is thought to be secondary to the low levels of circulating gonadotropins being suppressed by high inhibin and P levels. It is an interesting finding that CC, which is effective at the level of the hypothalamus, can induce follicle growth during this relatively hormonally quiescent state. A case of follicular growth in response to CC has recently been reported in the presence of an EP (5).

In the present report, we observed multiple follicular development in response to CC in spite of the presence of an undiagnosed ovarian EP. Interestingly follicular growth occurred bilaterally, including in the ovary, in which the EP was eventually diagnosed. This complicated the diagnosis further preoperatively as well as intraoperatively secondary to an absent mass in the adnexal region and a presumed corpus luteum (CL). Clinical presentation can be confusing, as we have previously experienced and reported a case of ovarian follicle development with a co-existing undiagnosed EP that clinically mimicked ovarian hyperstimulation syndrome (OHSS) (4). The important clue in these rare cases is that the initial β-hCG levels are almost always unexpectedly high. The β-hCG level at the time of missed menses in a normal pregnancy should be expected to be at a level of approximately 100 mIU/mL; in our patient it was more than 10,000 mIU/mL, indicating that the pregnancy had been established in the previous cycle. Note that day 3 levels of E_2 and FSH are not helpful in ruling out a preexisting ectopic gestation, as they were both in the normal range in this report. It is interesting to speculate that P levels might have been useful, although the cost-effectiveness of routine P determinations on day 3 is questionable.

In conclusion, CC can induce follicles to grow to the final mature stage in spite of the presence of a preexisting EP, and presumed concomitant high levels of β-hCG.

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