Inadvertent Superovulation and Intrauterine Insemination During Pregnancy: A Lesson from an Ectopic Gestation

Ho-Yen Chueh,¹ Po-Jen Cheng,¹ Chia-Woei Wang,^{1,2} and Yung-Kuei Soong

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It is believed that follicular development and ovulation is suppressed during the early period of gestation in humans. In this report, we describe a patient who underwent ovarian hyperstimulation following a "presumed" menstrual bleeding. The case illustrates that the ovaries during early pregnancy seem to respond normally to exogenous gonadotrophin stimulation. Despite ongoing pregnancy, the high plasma concentrations of gonadotrophins have rescued pituitary and ovarian insensitivity. Normal follicular development and even ovulation are allowed to occur. Moreover, it is mandatory to preclude pregnancy before commencing superovulation and assisted reproductive technology.

KEY WORDS: Controlled ovarian hyperstimulation; pregnancy; superovulation.

INTRODUCTION

It is believed that follicular development and ovulation is suppressed during the early period of gestation in humans. This is the reason why superfetation, a phenomenon that ovulation occurs during the course of an established pregnancy and results in another pregnancy and development of a fetus when at least one fetus is already present in the uterus, is extremely rare in humans.

In this report, we describe a patient who underwent ovarian hyperstimulation following a "presumed" menstrual bleeding. Normal follicular development was found after exogenous gonadotrophins and intrauterine insemination (IUI) was performed in this patient who finally was found to have an undiagnosed ectopic gestation.

CASE REPORT

The patient was a 31-year-old woman and represented a case of primary infertility of 7 years duration. The infertility workup was essentially negative, including normal hysterosalpingogram, hormonal assessment, and semen analysis. Her menstruation cycles were usually ovulatory and lasted between 28 and 30 days. She had undergone superovulation with clomiphene citrate and human menopausal gonadotropin (hMG; Pergonal, Serono Laboratories, Randolph, MA) followed by IUI for three cycles, but all failed to induce a pregnancy.

In this controlled ovarian hyperstimulation (COH) and IUI cycle, her presumed menstruation period began on Day 29 of her previous cycle with normal menstrual duration, amount, and appearance. Clomiphene citrate 100 mg/day from Day 3 to Day 7 and hMG 150 IU on Days 4, 6, 8, and 10 were administered for ovulation induction. On Day 12 of this cycle, human chorionic gonadotropin (Pregnyl, Organon, Oss, The Netherlands) 10,000 IU was given when two leading follicles were larger than 1.8 cm (Fig. 1) and the serum E2 level was 846 pg/mL. IUI was performed on Day 14. Four days following IUI, the patient presented with acute-onset lower abdominal

¹ Department of Obstetrics and Gynecology, Lin-Kou Medical Center, Chang Gung Memorial Hospital, 5 Fu-Hsing Street, Kwei-Shan, Tao-Yuan, Taiwan.

² To whom correspondence should be addressed at Department of Obstetrics and Gynecology, Lin-Kou Medical Center, Chang Gung Memorial Hospital, 5 Fu-Hsing Street, Kwei-Shan, Tao-Yuan, Taiwan; e-mail: cwwang@ms4.hinet.net.

Fig. 1. Transvaginal ultrasonography on Day 12 of the “presumed” menstrual cycle revealed a stimulated ovary measuring 5.0 cm × 3.1 cm with normal follicular development.

pain. A blood sample was withdrawn for β -HCG determination, and the concentration was found to be 6660 IU/mL. Transvaginal ultrasonography revealed moderate cul-de-sac fluid and enlarged stimulated bilateral ovaries, but there was no intrauterine gestational sac demonstrated. Under the impression of ectopic pregnancy, the patient was then treated with laparoscopic surgery. The laparoscopy disclosed a ruptured right ovarian cyst 3 cm in diameter and hemoperitoneum of 2400 mL. Laparoscopic wedge resection of the right ovary was carried out. The operation and postoperative recovery were uneventful. The pathology report revealed ovarian ectopic pregnancy.

DISCUSSION

It has been proved that the ovary is not overtly refractory to gonadotrophin stimulation during early pregnancy (1). The interruption of ovulatory function imposed by pregnancy seems to result from the suppression of the hypothalamic-pituitary gonadotrophin secretion, which is likely due to the high concentration of oestradiol, progesterone, and possibly inhibin in pregnancy. However, exogenous gonadotrophin can overcome this inhibition and leads to follicular growth, as in this patient, whose follicular development was found to be normal after being stimulated with clomiphene citrate and gonadotrophin in spite of a co-existing ectopic pregnancy. But a high progesterone state in pregnancy may turn hostile the function of the fallopian tubes and cervical mucus; Furthermore, decidual endometrium may also prevent subsequent embryo implantation even when

another ovulation occurs. It may explain that although superfetation is common in some species (2), only sporadic cases in humans have been described in the literatures (3–7). Most authorities believe that these alleged cases of human superfetation may result from marked inequality in growth and development of twin fetuses of the same gestational age (8). Nevertheless, small and undeveloped follicles obviously populate the ovaries in early pregnancy with functionally intact oocytes (9). It has been shown that oocytes retrieved during pregnancy can be fertilized (10) or even initiate a pregnancy (11).

This case illustrates some lessons to be learned. First, it seems plausible that the ovaries during early pregnancy seem to respond normally to exogenous gonadotrophin stimulation. Despite ongoing pregnancy, at least in ectopic pregnancy, the high plasma concentrations of gonadotrophins and hCG administration have rescued pituitary and ovarian insensitivity. Normal follicular development and even ovulation are allowed to occur.

Second, it is mandatory to preclude pregnancy before commencing superovulation and assisted reproductive technique (ART). It has been estimated that during early pregnancy, vaginal bleeding at about the time of the missed menstrual period may occur in as many as 8% of women (12), and has been referred to as a “physiological response to implantation.” Such bleeding, especially when all its characteristics are similar with normal menstruation, may be considered an indication of the new menstrual cycle and may be followed by another attempt of ART. Therefore, it is justified that in a patient preparing for ART cycles, all efforts should be made to rule out pregnancy before attempting another stimulation.

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