CASE REPORT

A documented clomiphene-induced follicular development in pregnancy

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A case of clomiphene-induced follicular growth in pregnancy is presented in a 34-year-old woman with ectopic pregnancy treated at a university teaching hospital. Following administration of clomiphene citrate in pregnancy, follicular growth to 18 mm mean diameter was noted. It is concluded that clomiphene citrate can induce follicular growth and maturation in pregnancy, possibly by reversing pregnancy-induced pituitary suppression.

Key words: clomiphene/follicle/pregnancy/superfetation

Introduction

It is believed that in humans, follicular development and ovulation is suppressed during the early period of gestation. In contrast, in some animal species spontaneous ovulation, pregnancy and subsequent development of a fetus when another fetus is already present in the uterus is a common occurrence (Caillol et al., 1991)—a phenomenon called superfetation. In this report, follicular development following administration of clomiphene citrate is described in a woman who harboured an ectopic pregnancy. The data show that clomiphene can reverse pregnancy-induced pituitary suppression.

Case report

A 34-year-old woman was first seen in March 2000, with secondary infertility of 7 years duration. Her menstruation was regular every 28 days. Infertility investigations revealed patent tubes on hysterosalpingogram and ovulatory mid-luteal phase progesterone. Her husband had normal semen analysis. The patient was advised to undergo superovulation with clomiphene citrate (Serophene; Serono Canada Inc., Oakville, Ontario, Canada; 50 mg daily for 5 days) and intrauterine insemination. Following standard practice, follicular development was monitored with transvaginal ultrasonography on the third or fourth day and on the ninth day of the cycle, and then on alternate days until the diameter of the dominant follicle reached a mean of 18 mm.

In the first cycle, a single dominant follicle of 20 mm was seen on day 13. Ovulation was triggered with human chorionic gonadotrophin (HCG) (Profasi; Serono Canada Inc., Oakville, Ontario, Canada; 10 000 IU s.c.). Intrauterine insemination was performed 24 and 48 h later. On day 26 of the cycle, the patient reported that her menstruation resumed. Transvaginal ultrasonography 4 days later revealed the absence of any ovarian cyst, and an endometrial thickness of 3.4 mm. The same regime of clomiphene treatment was administered. On day 14 of this cycle, transvaginal ultrasonography revealed three follicles of 13, 16 and 18 mm. The endometrial thickness was 6.1 mm. Ovulation was triggered with HCG, and insemination was performed as in the preceding cycle. On day 28 of the cycle, the patient presented with a 10-day period of vaginal spotting and mild low abdominal pain. A blood sample was withdrawn for β-HCG measurement, and the concentration was found to be 16 652 IU/ml. Subsequent transvaginal ultrasonography revealed a right tubal ectopic pregnancy with fetal cardiac activity compatible with 7 weeks gestation. The patient was then treated with laparoscopic salpingostomy. The operation and the postoperative recovery were uneventful.

Discussion

Superfetation has been described as a rare phenomenon (Caillol et al., 1991). The European hare, however, frequently utilizes superfetation to increase its reproductive performance. At the end of pregnancy, their frequency of mating increases leading to a LH surge. In this species, ovulation and superfetation occur in up to 60% of pregnant females. In humans, sporadic cases of superfetation have been described in the literature (Serafani et al., 1985; Sharma et al., 1987; Lefebvre et al., 1990; Dmowski et al., 1997), most of which are related to gonadotrophin administration. The diagnosis was based on an apparent discrepancy in fetal development, which could alternatively be explained by intrauterine growth restriction of one of the fetuses.
In early pregnancy, small and undeveloped follicles populate the ovaries (Govan, 1968). After 8–10 weeks gestation, follicular growth and atresia continue until term. The oocytes per se, however, are functionally intact. It has been demonstrated (Hwang et al., 1997) that immature oocytes retrieved from the ovary at the time of delivery can be fertilized and initiate a pregnancy.

The ovulatory quiescence is due to an inhibition of the pituitary during pregnancy, and this has been demonstrated by a decreased FSH and LH response to gonadotrophin-releasing hormone (GnRH) administration (Rubenstein et al., 1978). The suppression of gonadotrophin is likely due to the high concentration of oestradiol, progesterone and possibly inhibin in pregnancy. Exogenous gonadotrophin can overcome this inhibition however, leading to follicular growth.

Unlike gonadotrophin, which has a direct effect on the ovary, the primary site of action of clomiphene citrate is the hypothalamus (Kerin et al., 1985). In animal models, clomiphene also exerts an effect on the pituitary and directly stimulates gonadotrophin release, independent of its action on GnRH (Adashi, 1986). In the current patient, clomiphene induced follicular development and maturation in pregnancy, which suggests that—at least in ectopic pregnancy—clomiphene can reverse pregnancy-induced pituitary insensitivity. It is possible that pituitary suppression in women with abnormally implanted pregnancy is incomplete. A possible case of super- fertilization related to clomiphene citrate was previously published (Bsat and Seoud, 1987); however follicular development was not demonstrated, and the possibility of symmetrical intrauterine growth restriction could not be discounted.

It is concluded that clomiphene citrate can induce follicular growth and maturation in pregnancy, perhaps by reversing the pregnancy-induced pituitary suppression.

References


Received on December 8, 2000; accepted on March 7, 2001