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An Ectopic Pregnancy Masked by Follicular Initiation of Gonadotropin-Releasing Hormone Agonist for Pituitary Desensitization Prior to In Vitro Fertilization

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INTRODUCTION

Pituitary suppression by gonadotropin-releasing hormone (GnRH) agonists starting in either the midluteal or the early follicular phase has become a routine pretreatment before controlled ovarian hyperstimulation for in vitro fertilization (IVF). The administration of this long protocol of GnRH agonist increases the cumulative birth rate after IVF (1) and simplifies treatment by reducing the amount of monitoring necessary during ovarian stimulation (2). One of the disadvantages of commencing the administration of GnRH agonists in the luteal phase is interference with an unexpected pregnancy. At least 75 pregnancies and 49 deliveries following initiation of GnRH agonists in the luteal phase have been described in the literature (3). This risk cannot be eliminated, as serum β -hCG levels at the time of initiation of GnRH agonist administration in the midluteal phase are not sufficiently high to be detected by currently available hormone assays. In

theory if pituitary desensitization is started in the early follicular phase of the menstrual cycle, the risk of inadvertent administration of GnRH agonists in early pregnancy should not arise. However, here we report the first case of exposure of an early ectopic pregnancy to GnRH agonist therapy which was initiated in what was presumed to be the follicular phase of a menstrual cycle.

CASE REPORT

A 37-year-old woman with 16 years of primary infertility was referred to the McGill Reproductive Center for IVF treatment following an unsuccessful salpingostomy for bilateral hydrosalpinges. She had spontaneous regular ovulatory menstrual cycles and her husband's semen analysis was normal.

Transvaginal ultrasound performed on day 2 of the menstrual cycle showed normal bilateral ovaries, no cysts, and a normal uterus with a maximum endometrial thickness of 5 mm. The patient was started on the GnRH agonist, busurelin acetate (Suprefact; Hoechst-Roussel, Montreal), at a dose of 500 μ g/day administered subcutaneously. Transvaginal ultrasound was performed 10 days later, which revealed the presence of three ovarian cysts with average diameters between 25 and 30 mm in the right ovary, two cysts with diameters of 22 and 24 mm in the left ovary, and an endometrial thickness of 7 mm. The GnRH agonist was continued and an im injection of 100 mg progesterone was administered to precipitate a withdrawal bleed and hasten pituitary suppression (4) (Gesterol, E. L. Stickley Co, Brantford, Ontario, Canada). Seven days later a repeat ultrasound scan showed that the ovarian cysts had not regressed and the serum E_2 level was 2066 pM (conversion factor to SI units, 3.67). Although the dose of busurelin was increased to 500 μ g twice a day, the serum E_2 level was 3312 pmol/ml 1 week later and an ultrasound scan showed an endometrial thickness of 6 mm and the presence of one right ovarian cyst of 34-mm diameter and a left ovarian cyst of 39 mm. A decision was made to aspirate the cysts. An uneventful transvaginal ultrasound-guided bilateral aspiration of both ovarian cysts was performed, and 20 ml of clear fluid was aspirated from one cyst and a small amount of blood-stained material aspirated from the other ovarian cyst. The serum estradiol concentration 29 days after initiation of busurelin was 6152 pmol/ml. Ultrasound revealed the endometrial thickness to be 9 mm and the presence of a solid mass measuring $4.7 \times 2.8 \times 4.65$ cm in diameter in the region of the ovary.

Because of the increasing serum estradiol level and the ultrasound findings, the serum β -hCG level was measured and found to be 3330 IU/L. Because no intrauterine gestational sac could be identified on the ultrasound scan, an ectopic pregnancy was suspected and the patient underwent a laparoscopy the same day. A large unruptured ectopic pregnancy was noted in the ampullary region of the left fallopian tube. The ectopic pregnancy was removed by salpingotomy and the patient was discharged home the next day. Her post-operative course was uneventful.

DISCUSSION

The case described here is, to the best of our knowledge, the first report of a pregnancy being masked by follicular-phase initiation of GnRH agonists for pituitary desensitization prior to IVF. Most likely the patient conceived in the cycle prior to the treatment cycle, and the vaginal bleeding the patient experienced just before the administration of the GnRH agonist was probably bleeding in early pregnancy rather than normal menstrual bleeding. The ultrasound finding of a thin endometrium at that stage is consistent with recently published data showing that a considerable number of patients with abnormal early pregnancy have a thin endometrium (5). The ovarian cysts which formed during treatment were most likely due to the initial stimulatory effect of the GnRH agonist and are a common phenomenon. Unfortunately, the presence of the ovarian cysts masked the presence of the developing adnexal mass, and the absence of signs such as severe lower abdominal pain or the presence of fetal echoes on ultrasound scan considerably delayed the correct diagnosis. Fortunately, the rising serum estradiol concentration and the adnexal mass on ultrasound scan, which become apparent after the cyst aspiration, raised our suspicions of a possible ectopic pregnancy. This delay in establishing the diagnosis could have been critical.

In recent years, GnRH agonists have become widely incorporated into ovarian stimulation regimens for IVF. Different protocols have been designed for the administration of GnRH agonists. The long protocol is generally accepted to produce better results than the short protocol (6), and it has also been shown that when the long protocol is used, initiation of GnRH agonists in the early follicular phase results in less profound pituitary suppression, a larger number of oocytes collected, and possibly higher pregnancy

rates, compared with initiation of GnRH agonists in the midluteal phase (7).

An additional disadvantage of midluteal initiation of GnRH agonist administration is interference with early pregnancy. The risk of this complication is not negligible and rates of coincidental pregnancy of about 1% have been reported (3). Although no increased risk of fetal malformation connected with the administration of GnRH agonists in early pregnancy has been reported, animal data suggest that prolonged use of GnRH agonists in early pregnancy could cause fetal malformations (7).

The chance of accidental administration of GnRH agonist in an early pregnancy is extremely small if the GnRH agonist is initiated in the early follicular phase. Until now this has been considered only a theoretical possibility. In theory, such as the one described here could be avoided if all patients had a pregnancy test prior to starting GnRH analogue. However, the introduction of such a measure would require an additional visit to the hospital for all patients. Owing to the rarity of the condition, this measure seems to be unnecessary. However, the possibility of ectopic pregnancy should be borne in mind if the serum estradiol concentration rises despite continued administration of the GnRH agonist. Timely intervention is important to avert the potentially serious complications resulting from rupture of an ectopic pregnancy.

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