Oocyte retrieval following continued stimulation five days beyond ovulation yields live birth after frozen embryo transfer

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Introduction

There is often a narrow time window for cancer patients to accomplish fertility preservation before cancer treatment initiation. Despite attempts at pituitary blockade, premature ovulation prior to oocyte retrieval may occur. In that situation, conventional practice dictates cancellation of the cycle. There is no existing literature regarding oocyte quality and yield in stimulated cycles in which ovulation occurs in the early follicular phase prior to hCG trigger. Here we report a case of continued ovarian stimulation 3 days beyond documented ovulation in a woman with breast cancer, with the cycle yielding embryos

capable of resulting in a successful twin pregnancy after transfer to a gestational surrogate.

Case report

A 40-year-old gravida 1 para 0 who had recently undergone bilateral mastectomy for invasive ductal carcinoma desired fertility preservation prior to chemotherapy and prophylactic bilateral salpingo-oophorectomy. She planned to take adjuvant hormonal therapy for 5 years given the positive hormone receptor status of her tumor, and therefore decided to use a gestational surrogate. She reported regular menses and no significant gynecologic history. Her past medical history was notable only for early stage thyroid cancer, which was treated successfully with thyroidectomy alone in 2009.

The patient presented cycle day 16 of her menstrual cycle. As there are limited data on starting stimulation in the late follicular/luteal phase, we elected to induce menses and start stimulation as conventionally performed in the early follicular phase. Therefore, GnRH antagonist (Ganirelix; Schering-Plough, Kenilworth, NJ) was administered cycle day 16 through cycle day 19, with menses starting on the fourth day of antagonist. Of note, prior to GnRH antagonist administration a progesterone level was checked and was found to be 0.7 ng/ml, indicating that ovulation had not yet occurred. Baseline estradiol level was 114 pg/ml.

Baseline ultrasound performed cycle day 2 noted no cysts and six antral follicles in the right ovary and four in the left ovary. Ovarian stimulation was initiated with recombinant FSH 300 IU/d (Follistim; Schering-Plough, Kenilworth, NJ), highly purified hMG 150 IU/d (Menopur; Ferring Pharmaceuticals, Parsippany, NJ) and tamoxifen 60 mg daily.

On cycle day 6 (day 5 of stimulation), a 21 mm follicle was seen and GnRH antagonist was started. All other follicles

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Capsule A 40-year-old with breast cancer underwent retrieval five days after ovulation and frozen embryo transfer to gestational surrogate resulted in live birth of twins. Continuous ovarian stimulation despite ovulation can yield embryos capable of resulting in viable pregnancy.

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at that time were ≤ 11 mm. On cycle day 7, there was a cyst that appeared to be a corpus luteum as well as a cohort of smaller developing follicles, the largest being 13 mm. Progesterone level drawn on cycle day 7 was elevated (3.8 ng/ml) and was noted to increase further the following day (5.7 ng/ml). Despite confirmation of ovulation, GnRH antagonist and ovarian stimulation was continued given the second cohort of follicles seen and the patient's limited time window prior to starting chemotherapy. Of note, the patient was counseled that standard practice in the setting of premature ovulation is cycle cancellation, however, as she did not have time to start another cycle, she elected to continue stimulation. By cycle day 9, progesterone was persistently elevated (4.4 ng/ml), but there were multiple follicles growing, with five follicles ≥ 17 mm.

Human recombinant chorionic gonadotropin (hCG) trigger (Novarel; Ferring Pharmaceuticals, Parsippany, NJ) was given and 35 h later on cycle day 11, transvaginal oocyte retrieval was performed, yielding 14 normal appearing cumulus oophorus complexes. Standard insemination was performed. The semen analysis from her partner showed a volume of 2.5 mL, concentration of 71.5 million/mL, and 70% motility, with a post wash specimen of 1.2 mL, 32 million/mL and 86% motility. Fertilization was assessed the day following insemination, and nine 2-pronuclei embryos and one 1-pronuclei embryo were cryopreserved using vitrification.

Six months after cryopreservation, six 2-pronuclei embryos were thawed. Two days later, three cleavage-stage embryos (8-cell grade II, 8-cell grade III and 3-cell grade II) were transferred to a gestational surrogate. Serum bHCG was positive 10 days later and ultrasound at 8 weeks gestation showed a viable twin pregnancy. The surrogate subsequently delivered two healthy male infants at 38 weeks gestation, weighing 6lb12oz and 7lb4oz.

Discussion

This case is to our knowledge the first to describe continued ovarian stimulation after ovulation with oocyte retrieval, embryo cryopreservation and subsequent successful frozen embryo transfer. Due to the inhibitory influences of luteal progesterone, it has been suggested that limited follicular development can occur in the luteal phase and that the corpus luteum may negatively impact neighboring follicular growth [1]. Other investigators, however, have demonstrated that there are often several waves of ovarian follicular growth within each menstrual cycle, and that follicles developing in the luteal phase are capable of ovulating in the presence of an LH surge [2, 3].

There have been a handful of publications suggesting that luteal phase stimulation can yield mature oocytes and good quality embryos comparable to standard initiation of stimulation [4, 5]. Some concerns remain with luteal phase stimulation regarding the potential impact of elevated progesterone levels on oocyte quality and endometrial receptivity. The effects of premature luteinization in IVF cycles remain controversial, with many studies suggesting lower success rates [6, 7], and other studies failing to find a negative impact on outcomes [8, 9]. This case differs from standard luteal phase stimulation in that ovulation occurred during ovarian stimulation prior to hCG trigger.

In conclusion, this case illustrates that continued ovarian stimulation after ovulation can yield embryos capable of resulting in a live birth. Although the progesterone rise resulting from premature ovulation may have negatively impacted endometrial receptivity, in this case of urgent fertility preservation, we chose to continue stimulation. Elevated progesterone concentrations do not appear to have been detrimental to oocyte quality as the cycle yielded embryos that resulted in a successful twin pregnancy. The outcome in this case suggests that despite ovulation several days prior to hCG trigger, if there is a cohort of smaller follicles growing, patients should be offered continued ovarian stimulation for oocyte retrieval. Thus, ovulation prior to retrieval need not uniformly necessitate cycle cancellation, especially in the case of urgent fertility preservation.

Conflicts of Interest/Financial support None

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