IVF stimulation in pregnancy: lessons to be learned with implications for the luteal phase start IVF cycle

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Dear editor,

In vitro fertilization (IVF) has been widely used to treat infertile couples. Standardly, IVF protocols start stimulation in the early follicular phase [1]. Centers routinely perform ultrasound on cycle day 2 to 3 to evaluate the endometrial lining, rule out pregnancy, and verify a lack of functional ovarian cysts before starting controlled ovarian stimulation. However, the role of early follicular start is being questioned, with random and luteal phase stimulations being investigated, particularly in centers practicing freeze all protocols to favor implantation [1–3]. This is done for both convenience and in cancer patients desiring pre-chemotherapy fertility preservation, who must start urgently [4, 5]. In a recent study, patients were divided into three groups based on menstrual cycle phase for commencement of stimulation: the conventional early follicular, late follicular phase, and luteal phase starts. All three groups were comparable in terms of the number of mature oocytes (MII), quantity of embryos and oocytes retrieved, implantation rates, and clinical pregnancy rates [2]. Clearly, a random start for IVF stimulation is interesting in that it will minimize time to initiate stimulation, particularly if the center will perform pre-implantation genetic testing type A or for implantation benefit, freeze all embryos, a trend, which is increasing, particularly in the USA.

However, when luteal phase starts, one complication that may arise is that the patient could be unknowingly pregnant. The role of pregnancy on stimulation outcomes has not been investigated. However, we would anticipate that the body has mechanisms in place to prevent double fecundation at different time periods, which would result in two pregnancies of different gestational ages developing concurrently. The role of

such mechanisms on oocyte potential is unknown. Clearly, if a patient starts stimulation that may last 10 to 14 days, 7 days before a menses is anticipated, and she is unknowingly pregnant, even a pregnancy test at this time may not be positive. However, we suspect few centers perform routine pregnancy tests before luteal phase start of IVF cycles.

Recently, a patient taught us about ovarian stimulation in pregnancy. A 35-year-old was diagnosed with triple negative breast cancer. Two days post diagnosis, the patient discovered she was pregnant. She was referred to the fertility center at 4 to 5 weeks of gestation, for fertility preservation and to arrange a termination of pregnancy. She had no other medical conditions or previous surgeries. The patient was given the options of freezing oocytes or embryos since she had a long-term partner and the couple decided to freeze embryos.

Transvaginal ultrasound demonstrated a single intrauterine sac (IUGS) with yolk sac (YS); the fetal pole was not yet visible. The right ovary had only one antral follicle while the left ovary had six antral follicles. The patient was then started on mifegymiso (mifepristone/misoprostol), one tablet orally followed by 800 mcg of misoprostol 36 h later. On the same day, controlled ovarian hyperstimulation was started with Puregon (FSH) 300 IU and Luveris (LH) 75 IU, both subcutaneously. Letrozole 10 mg orally was added on a daily basis to prevent a rise in serum estradiol levels, possibly exacerbating the breast cancer. The patient was seen on day 6 of ovarian stimulation. Ultrasound showed no ovarian response. There was still an intrauterine pregnancy. The serum beta-HCG level was 11,099 IU/L. Controlled ovarian stimulation was continued. After another 2 days, a dilatation and curettage was performed. The patient was seen 1 day after termination of pregnancy on day 13 of stimulation. There were seven follicles between 14 and 20 mm and four 12-mm follicles. The rest were smaller. Serum beta-HCG was 3100 IU/L. The patient was triggered with 1000 mcg of Suprefact and 5000 IU of HCG. Oocyte collection was performed 36 h after triggering. At collection, many follicles released no oocytes. Five oocytes were collected in total. All collected oocytes had an abnormal

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appearance, are dark with granulations, and had luteinized cumulus cells. Stripping was done and the stage of the oocytes was determined. In spite of the follicular size, four oocytes were metaphase I (MI) stage, and one was degenerated. Given that lack of mature oocytes, in vitro maturation (IVM) was performed using global total culture IVM media with Repronex 75 mIU/ml added. The following day, there were four metaphase II (MII) oocytes. Intra-cytoplasmic sperm injection (ICSI) was performed; however, there was no normal fertilization. Of four embryos that occurred, there were a 4PN, a 3PN, and two 0PNs. No further cycles were performed as the patient started chemotherapy the day after oocyte collection.

I discussed this case at a lecture on random start IVF at the Fertility Academy meeting in Madrid, Spain, in March 2019. I asked the speaker if they have considered that some women with luteal phase starts will be pregnant and the implications for the IVF cycle outcomes. I asked if they consent women with luteal phase starts for the possibility of pregnancy and implications on that pregnancy. It was clear that these possibilities raised a great deal of debate in the room and require a published discussion. Clearly, the outcome of the above discussed IVF cycle is far from ideal. Few oocytes were collected compared with the number of follicles, in vivo maturation arrest seemed to be present in those oocytes that were collected, and even though the oocytes matured in vitro, they seemed to have no potential to develop into a normal embryo. Those embryos that did develop had abnormal genetic components as demonstrated by an abnormal quantity of pronuclei that would preclude development into a baby. A question arises if this was due to the concurrent use of letrozole or the anti-progestin. This does not seem likely. We often give concurrent letrozole to fertility preservation patients with breast cancer to limit serum estradiol levels and advancement of the tumor [6]. Oocytes develop normally with normal collection components and normal fertilization occurring. Although anti-progestins (RU-486) could interfere with implantation [7], this was not an issue in this case, since embryos were being frozen. The use of high-dose progestin to prevent the LH surge for oocyte collection instead of a GnRH agonist in other studies has been demonstrated to not affect the quality and quantity of oocytes retrieved or embryos [8, 9]. Concurrently, it can be deduced from these studies that lower progesterone levels also result in similar quality and quantity of oocytes as high levels; therefore, the anti-progesterone was unlikely to have an effect.

It makes inherent sense that the oocytes were compromised. Few were collected because the body would wish to prevent fertilization at a second point during a pregnancy. If this occurred, it could result in premature delivery of a second twin when the first older gestation goes into labor. Those oocytes that did occur were immature further preventing fertilization and had no potential to develop into a pregnancy, even when matured. The stimulation of concurrently pregnant women should be a consideration in random start cycles

particularly those in the luteal phase, as a possible complication. At the beginning of the stimulation, it could be too early to detect the pregnancy, which would only demonstrate itself near the end of the cycle. It is not unheard of to have fertility patients conceive spontaneously while awaiting IVF or after cycles, with most physicians having experienced such a situation [10, 11]. In the least, consents of random start subjects should have such a possibility listed, and all subjects should have a serum beta-hCG level drawn. It is likely such oocytes would have a low potential for pregnancy. This needs to be addressed with the patients. The subject in this case was 5 weeks pregnant when the stimulation was started. It is possible that had she been less pregnant, a different outcome could have occurred. However, we are familiar with a second unpublished case of a stimulation, which occurred in the late luteal phase and a sac was noted in the uterus of at most 5 weeks gestation age at the time of collection. In this case, oocytes were collected and embryos made. The subject subsequently miscarried and frozen embryo transfers were performed. Those embryos appeared grossly normal; however, multiple transfers failed to give a pregnancy when they were subsequently used, again, resulting in a question of competency of the oocytes when stimulating patients during a concurrent pregnancy, even if it is in very early gestation.

In conclusion, in luteal phase and random start IVF a concurrent pregnancy and resultant effect on oocyte and embryo potential should be considered and discussed in advance with the patients. Concurrent pregnancy likely has an adverse effect on oocyte potential and will possibly prevent a pregnancy from embryos stimulated during such.

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