Fertility preservation in an oncology patient who presented with positive human chorionic gonadotropin

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Objective: To report the case of a woman who presented for fertility preservation before breast cancer treatment who was found to be pregnant with an undesired pregnancy.
Design: Case report.
Setting: Single infertility practice.
Patient: A 28-year-old woman with a new diagnosis of grade 3 invasive ductal carcinoma of the breast was planning to undergo oocyte cryopreservation and was found to be pregnant with an undesired pregnancy. She underwent a medical termination at a gestational age of 5 weeks 4 days. Neither the patient nor her oncology team wished to delay treatment more than was necessary. The physician and patient decided to initiate controlled ovarian hyperstimulation (COH) before her human chorionic gonadotropin (hCG) returned to normal.
Intervention(s): COH in the setting of a positive quantitative hCG.
Main Outcome Measure(s): Number of metaphase II (MII) oocytes cryopreserved; doses of Gonal-F and Menopur; serum E_2, follicle-stimulating hormone, luteinizing hormone, hCG levels.
Result(s): COH began 7 days after passing the products of conception. Baseline labs demonstrated hCG at 222 mIU/mL, follicle-stimulating hormone at <0.10 mIU/mL, luteinizing hormone at <1.10 mIU/mL, and E_2 at 147 pg/mL. She was started on an antagonist protocol with the use of 150 IU Gonal F and 75 IU Menopur. She was triggered on stimulation day 14 with 5,000 U hCG, and her peak E_2 was 5,924 pg/mL. She ultimately had 18 oocytes retrieved, 12 of which were MII, one MI, and five germinal vesicle. All were vitrified.
Conclusion(s): COH can be achieved in the setting of low positive hCG levels with subsequent successful oocyte maturation. The threshold for hCG trigger to be ineffective in the setting of a positive hCG has yet to be determined. (Fertil Steril Rep® 2020;1:51–3. ©2020 by American Society for Reproductive Medicine.)
Key Words: Ovarian stimulation, fertility preservation, pregnancy

In the field of reproductive endocrinology and infertility, pregnancy is routinely ruled out before starting a treatment cycle. If a positive human chorionic gonadotropin (hCG) level is identified, the patient is usually pleasantly surprised and treatment is postponed. However, in the setting of treatment for fertility preservation, pregnancy may not be desired. When patients present for fertility preservation and are found to have an unanticipated positive hCG, new concerns arise.

This scenario is even more difficult when the patient is pursuing fertility preservation after a recent cancer diagnosis. It is currently recommended that patients be counseled regarding fertility preservation before receiving gonadotoxic treatment (1, 2). Although most oncologists now recognize this as an important part of caring for the oncology patient, many are reluctant to delay treatment (2, 3). Fertility preservation for oncology patients is typically a time-sensitive matter, and many patients are limited to one or two cycles of controlled ovarian hyperstimulation (COH) before receiving gonadotoxic treatment (4, 5). We present the case of a young woman who presented to our clinic for fertility preservation after a recent diagnosis of

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triple-negative breast cancer who was found to be pregnant with an undesired pregnancy. There have been reports of successful COH in patients who were subsequently found to have a positive hCG (6–8) as well as in pregnant nonhuman primates (9). However, this is the first reported case of intentional COH in a patient with a positive hCG.

MATERIALS AND METHODS

Informed consent was obtained from the patient for the publication of this case report. The patient was 28 years old, gravida 0, with a medical and surgical history only notable for appendectomy, and had discontinued combined oral contraceptive pills 7 months before her presentation. She was diagnosed with grade 3 invasive ductal carcinoma of the left breast 3 days before her consultation for fertility preservation. The breast biopsy demonstrated triple-negative (estrogen receptor negative, progesterone receptor negative, and Her2 negative) breast cancer with positive lymphovascular invasion. Her planned treatment was neoadjuvant chemotherapy, radiation, and surgery. She had no family history of breast cancer.

At the time of her consultation, she reported regular menses every 28 days. The patient decided to proceed with oocyte vitrification for fertility preservation and planned to initiate the cycle with her next menses, which was due in 2–3 days. Owing to the aggressive nature of her breast cancer, both the patient and her oncologist hoped to initiate chemotherapy as soon as possible. When the patient's menses did not start as expected, she took a home pregnancy test, which was positive. Although she was in a committed relationship, the pregnancy was undesired. She was referred to an outside provider where she was treated with mifepristone and misoprostol at a gestational age of 5 weeks and 4 days, as calculated from the last menstrual period, and she passed the products of conception uneventfully. Laboratory tests performed 3 days later revealed an hCG level of 1,177 mIU/mL, luteinizing hormone (LH) <0.10 mIU/mL, follicle-stimulating hormone 0.10 mIU/mL, and E_2 470 pg/mL. On ultrasound performed the same day, the patient had an antral follicle count of 23 and an endometrial thickness of 9 mm.

An extensive discussion was had with the patient regarding risks, benefits, and alternatives to proceeding immediately with COH before hCG returned to <5 mIU/mL. Although her quantitative hCG was expected to decrease, neither the patient nor her oncology team wished to delay her treatment any more than was absolutely necessary. The physician and patient decided to initiate COH before her hCG returned to normal.

RESULTS

COH began 7 days after passing the products of conception. Baseline laboratory tests demonstrated an hCG level of 222 mIU/mL, follicle-stimulating hormone <0.10 mIU/mL, LH <1.10 mIU/mL, and E_2 147 pg/mL. Antimüllerian hormone, baseline progesterone, and inhibin B levels were not measured. The patient was started on an antagonist protocol with 150 IU Gonal-F and 75 IU Menopur. Her stimulation protocol and corresponding laboratory values are presented in Table 1. On the day of trigger, her E_2 level was 5,924 (pg/mL) and she was triggered with 5,000 U hCG. Given that the patient's breast cancer was estrogen-receptor and progesterone-receptor negative, letrozole was not prescribed. She ultimately had 18 oocytes retrieved, 12 of which were metaphase II, one metaphase I, and five germinal vesicle. All were vitrified.

DISCUSSION

This is the first case reported of a patient undergoing COH in the setting of a known positive hCG after an elective termination of pregnancy. Her hCG did not reach a value <5 mIU/mL until day 14 of stimulation, suggesting that the fertility preservation process was expedited by approximately 2 weeks by initiating COH before her hCG normalized. Given the patient's success (18 oocytes retrieved, 12 of which were MII), this may be a reasonable approach for other women who find themselves in a similar scenario and in whom fertility preservation cannot be delayed.

It remains unknown whether an elevated hCG during COH affects the resumption of meiosis, either at the time of trigger or before actual trigger is administered. Is there the potential for premature oocyte maturation in the setting of

TABLE 1

Patient's stimulation protocol and corresponding laboratory values.

	Day of stimulation													
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/hCG trigger**
Gonal-F, IU	150	150	150	225	225	225	225	225	150	150	112.5	112.5	75	
Menopur, IU	75	75	75	75	75	75	75	112.5	112.5	112	112	112	75	
Cetrotide, mg								0.25	0.25	0.25	0.25	0.25	0.25	0.25
E_2, pg/mL				105		236		729	1522	1861	2858	3774	4982	5924
Progesterone, ng/mL				0.39		0.5		0.29	0.41	0.49	0.85	0.82	0.83	1.3
LH, mIU/mL				0.53		0.53		2.84						0.62
hCG, mIU/mL				36		19		14	11	8	7	6	5	<5

Note: hCG = human chorionic gonadotropin; LH = luteinizing hormone.

Carpinello. COH in a patient with a positive hCG. Fertil Steril Rep 2020.

elevated endogenous hCG after COH, or is the resumption of meiosis solely dependent on a surge? In addition, would an hCG trigger induce a surge sufficiently large enough to resume meiosis in the presence of an elevated endogenous hCG level? Fortunately, our patient's hCG normalized by the day of trigger. Thus, an hCG trigger could be used without having the answers to these questions.

However, in reports of unintentional COH during pregnancy, fertilization of retrieved eggs was much lower than expected: two of five oocytes fertilized in the case of an ectopic pregnancy, and three of eight oocytes fertilized in the case of a intrauterine pregnancy (6, 7). Oocyte maturity was not reported. Therefore, it is unclear whether fertilization failed to occur because the oocytes were immature (suggesting an insufficient trigger) or whether the oocytes were mature and simply failed to fertilize. In both cases, the patients' quantitative hCG levels were 200–285 mIU/mL on the day of trigger. Given that the patients had not yet ovulated, we can conclude that an hCG in the range of 200–300 mIU/mL is unlikely to induce premature maturation and that an hCG trigger does work at this level. However, it is unclear how higher levels of hCG affect oocyte maturation and fertilization, if at all.

In patients with time constraints for initiating fertility preservation, there is a fine balance between maximizing the number of oocytes and avoiding the risk of ovarian hyperstimulation syndrome (OHSS), which could delay the start of oncologic treatment. Leuprolide acetate trigger is of great utility in such a setting. However, in this particular case, a leuprolide trigger may not have been effective owing to the hypothalamic-pituitary suppression of endogenous gonadotropins in pregnancy. Indeed, this patient's baseline LH level was <0.10 mIU/mL, and the LH level on the day of trigger was only 0.62 mIU/mL. Therefore, the decision was made to proceed with an hCG trigger to minimize the risk of a failed trigger. Though not performed in this case, a different approach in those at high risk of OHSS would be to proceed with the use of a leuprolide acetate trigger and to check post-trigger progesterone and LH levels. If those demonstrated an inadequate response, then retriggering with the use of hCG could be performed at that point. Although gonadotropin secretion is inhibited during pregnancy, it is unclear whether there is continued gonadotropin storage. Although there is some evidence that LH storage persists in rats during pregnancy, a contrasting study demonstrated complete lack of LH response to GnRH stimulation by the fifth week of gestation in humans (10, 11).

Because of suppressed gonadotropins during pregnancy, we considered that she may respond to stimulation similarly to a patient with hypothalamic hypogonadism. Although her endogenous hCG would have likely provided some LH activity on the ovaries, the extent to which this activity would be sustained with decreasing hCG levels was unclear. This hypothesis was somewhat consistent with her performance. Her stimulation was slightly longer than average, with trigger administered on day 14. Baseline gonadotropin levels were very low, and her day 4 and day 6 E_2 levels reflected a suboptimal response to stimulation. Similarly, once she did respond, she did so robustly and her dosage ultimately needed to be decreased (Table 1). Contrastingly, both Serafini et al. and Diamond et al. did not demonstrate an increase in stimulation duration in their reports (6, 7). This could be due to increased LH activity from higher serum hCG levels. However, because no specific values were reported other than on the day of trigger, it is unclear whether that is a plausible explanation.

CONCLUSION

Combined ovarian hyperstimulation can be achieved in the setting of low positive hCG levels with subsequent successful oocyte maturation. However, until we can answer the questions surrounding oocyte maturation, we are less likely to be successful in those with high hCG levels. The threshold for hCG trigger to be ineffective in the setting of a positive hCG has yet to be determined.

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