

A live birth with unexpectedly low serum human chorionic gonadotropin level on day 11 after blastocyst embryo transfer: a case report

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Objective: To report a very rare case of live birth with unexpectedly low serum hCG level on day 11 after blastocyst embryo transfer.

Design: Case report.

Setting: Private infertility center.

Patient(s): A 30-year-old nulliparous woman presented with PCOS and 1 year of infertility.

Interventions(s): Conventional IVF was scheduled and a long-acting agonist protocol was selected.

Main Outcome Measure(s): Maternal serum hCG levels and transvaginal ultrasound exams for the embryo's well-being.

Result(s): The hCG level was 11.6 IU/L on day 11 after the transfer of two blastocyst embryos, which was considered as either failing or extrauterine pregnancy. After blood titration, there were delayed hCG increases. A series of transvaginal ultrasounds also indicated a delayed but normal-appearing intrauterine pregnancy. A healthy baby boy was delivered at term by means of cesarean section.

Conclusion(s): A low initial serum hCG level may be associated with certain maternal or fetal characteristics and IVF treatment variables. Close conservative observation is warranted before undertaking any therapeutic intervention. (*Fertil Steril Rep*® 2020;1:48–50. ©2020 by American Society for Reproductive Medicine.)

Key Words: Blastocyst embryo transfer, human chorionic gonadotropin, viable pregnancy

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Human chorionic gonadotropin (hCG), produced and secreted by the syncytiotrophoblast cells, is the unique and earliest reliable marker for embryo implantation. The rate of rise of hCG in in vitro fertilization (IVF) pregnancies is similar to that in spontaneous conceptions (1). The median hCG concentration on day 12 after embryo transfer was 126 IU/L in viable pregnancies and 31 IU/L in

nonviable pregnancies ($P < .0001$) (2). At levels below that minimum threshold, a nonviable pregnancy, either failing or extrauterine, would be highly suspected. However, certain maternal or fetal characteristics, as well as IVF treatment variables, may affect the initial hCG levels. Here, we report a live birth with an unexpectedly low serum hCG level (11.6 IU/L) on day 11 after blastocyst transfer.

MATERIALS AND METHODS

A 30-year-old nulliparous woman presented to our fertility clinic complaining of an inability to conceive for 12 months. Hysterosalpingography 2 years earlier revealed that one fallopian tube was obstructed and the other was partially obstructed. She had irregular periods, with an interval of 25–50 days. She had no clinical signs of hyperandrogenism, and her body mass index (BMI) was 25.39 kg/m². The sex hormone assay on day 5 of the menstrual cycle showed an LH-FSH ratio of 14.67:4.28 and testosterone level of 0.68 ng/mL (reference range 0.084–0.481 ng/mL). The transvaginal sonography revealed polycystic ovarian morphology. Semen analysis for the 32-year-old male partner was normal. The initial diagnosis was tubal-factor

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Q.Z. and S.X. should be considered similar in author order.

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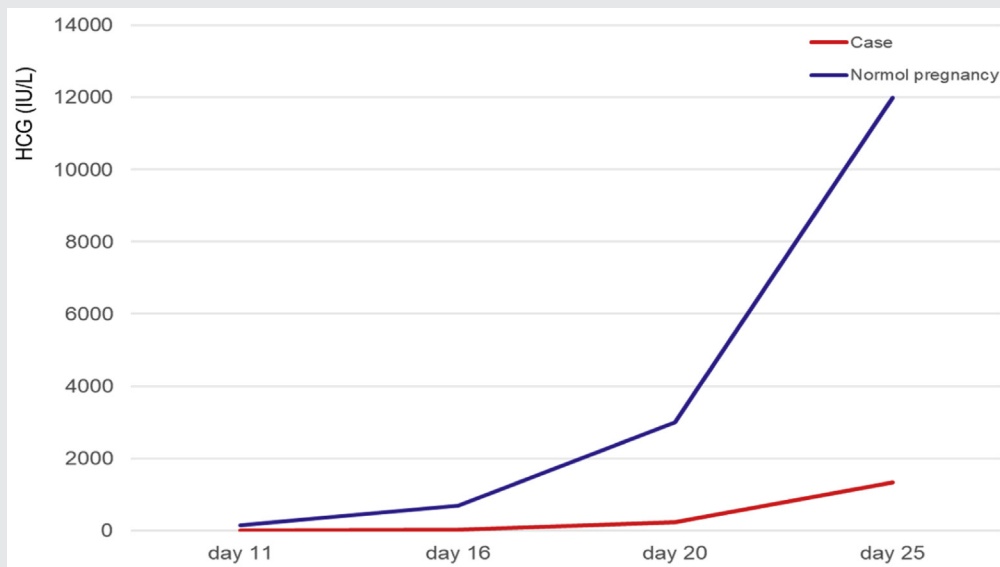
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FIGURE 1



Serum hCG changes in this case compared with normal pregnancy.

Zheng. Live birth with low initial hCG after ET. Fertil Steril Rep 2020.

infertility and anovulation secondary to polycystic ovarian syndrome.

After clinical assessment, the couple was scheduled for IVF and written informed consent was obtained. A long agonist protocol was initiated with the use of day 2 administration of a single dose of long-acting GnRH analogue (3.75 mg Decapeptyl CR; [Ipsen Pharma Biotech, Signes, France]). After 29 days, controlled ovarian hyperstimulation was started with the use of 150 IU recombinant FSH (Gonal F; Merck Serono, Rome, Italy) daily and monitored by transvaginal sonography, and the dose of gonadotropin was adjusted according to follicle size and number. Ovulation was triggered on ovarian stimulation (OS) day 10 with the use of 10,000 IU hCG as the mean diameter of three leading follicles reached 18 mm. The E_2 concentration on the day of hCG administration was 1,243.0 pg/mL, and progesterone was at 1.0 ng/mL. Fourteen oocytes were retrieved by means of transvaginal aspiration and ten were fertilized by means of IVF. Six embryos reached the blastocyst stage of development, and two blastocyst embryos (both grade A) were transferred.

RESULTS

Serum hCG on day 11 after embryo transfer was at 11.6 IU/L. According to previous statistics of our center, there was no normal pregnancy when the serum hCG level was <30 IU/L on day 13 after cleavage-stage embryo transfer or on day 11 after blastocyst transfer, so the physician stopped the routine luteal supplementation of 90 mg progestin (Crinone; Merck, Darmstadt, Germany) vaginally and 20 mg progestin tablets (Duphaston; Abbott, Weesp, Netherlands) orally daily. But serum hCG on day 16 after embryo transfer was increased to 40.1 IU/L, and on day 20 after embryo transfer to 247.3 IU/L.

The serum hCG changes in this case compared with normal pregnancy are shown in Figure 1. Also, transvaginal sonography showed a dark anechoic space measuring 2×1 mm in the uterus. Serum hCG on day 25 after embryo transfer was 1,332.3 IU/L, and transvaginal sonography showed a gestational sac of 5×3 mm, without yolk sac and fetal pole. Transvaginal sonography performed on day 28 after embryo transfer showed a gestational sac of 5×6 mm and a yolk sac without a fetal pole. Transvaginal sonography on day 31 after embryo transfer showed a gestational sac of 9×8 mm and a fetal pole of 4 mm with visible heart beat, and routine luteal supplementation as described previously was restored. Transvaginal sonography performed 38 days after embryo transfer showed a fetal pole of 10 mm with visible heart beat, which indicated a normal-appearing 8-week intrauterine pregnancy. Transvaginal sonography performed on day 52 after embryo transfer showed a fetal pole of 24 mm with visible heart beat, which indicated a normal-appearing 10-week intrauterine pregnancy. In June 2017 the woman underwent a selective cesarean-section delivery of a healthy male baby weighing 3,000 g.

DISCUSSION

Human chorionic gonadotropin is a pregnancy hormone produced by the placental syncytiotrophoblastic tissue. hCG can be detected in the maternal plasma as early as 8 days after fertilization, and it increases dynamically until a plateau at 100,000 IU/L by 10 weeks of gestation (3, 4). This typical trajectory of hCG is unique and makes it the most reliable predictor of early pregnancy outcomes. An initial hCG level lower than the minimum threshold suggests failing or extrauterine pregnancy. According to the American College of

Obstetricians and Gynecologists, the expected rate of increase in 48 hours is 49% for an initial hCG value <1,500 IU/L and 40% for an initial hCG level of 1,500–3,000 IU/L (4). An hCG increase <66% in 2 days during early pregnancy was characteristic of nonviable gestations (5). Although the initial serum hCG level was low in this case, the slope of hCG rise remained normal. This suggests that a linear increase in log hCG is more reliable in evaluating a viable pregnancy.

A previous study found that certain maternal or fetal characteristics, as well as IVF treatment variables, may affect initial hCG levels (6). A low initial hCG level may be associated with maternal obesity, smoking, nulliparity, male fetus, and decreased placental weight. In the present case, the BMI of the patient was 25.39 kg/m², which was overweight according to the Asian standard (7). Moreover, she was nulliparous and the fetal sex was male. All of these characteristics may have contributed to the low initial hCG level. Chung et al.'s work revealed that BMI has no impact on the rate of rise over time but can affect the absolute values of serum hCG (1), which was in accordance with our case.

Uterine receptivity refers to the capability of the endometrium to allow embryo implantation. Evidence showed that endometrial receptivity is affected by the type of OS. There is a slight advantage in favor of the long protocol in IVF patients with low initial hCG levels of <150 IU/L ($P = .03$) (3). Integrin $\beta 3$ subunit and leukemia-inhibitory factor (LIF) are two cellular factors that appear in the endometrium coinciding with the implantation window, and they are largely accepted as promising biomarkers of uterine receptivity in both human and mice (8). A previous study indicated that OS with the use of GnRH agonist (GnRH-a) cotreatment increased the expression levels of endometrial integrin $\beta 3$ subunit and LIF and the implantation rate, but not with GnRH antagonist cotreatment, suggesting an improved uterine receptivity in the long agonist protocol (9). High E_2 levels during OS lead to premature progesterone elevation, causing endometrial advancement and hampering implantation (10). A long agonist protocol is capable of achieving pituitary desensitization and suppresses the premature progesterone elevation. As administration of higher doses (3.75 mg depot) of long-acting GnRH-a provides a deeper suppression compared with a low dose (0.1 mg) of GnRH-a daily (11), thus may further decrease the E_2 level and improve uterine receptivity. In the present case, the E_2 level on the day of hCG administration was 1,243.0 pg/mL, which is much lower than in routine cases.

Tur-Kaspa et al. (12) found that the hCG regression curve for the GnRH-a/hMG pregnancies revealed a delay of 1.5 days in estimated implantation time compared with the hMG-only group, and a GnRH-a/hMG stimulation protocol appeared to widen the implantation window compared with an hMG-only protocol. It is plausible that the extended implantation window in the long-acting GnRH-a protocol improved the pregnancy outcome in the present case.

Embryo status is another key factor in a successful implantation. Is there an effect of embryo morphology on serum hCG levels? A recent study revealed that there was no difference in day 12 hCG levels after the transfer of a single fresh blastocyst or cleavage-stage embryo, whereas hCG level correlated with day 5 blastocle expansion and blastocyst quality score in ongoing pregnancy and live birth (13). In the present case, both of the two blastocyst embryos transferred were grade A (3BB, 4AB), and the effect of the embryo on hCG levels may be excluded.

Although this is a rare case, the finding is clinically significant. Certain maternal or fetal characteristics, as well as IVF treatment variables, may affect the hCG levels. In the case of an unexpectedly low serum hCG level but with a normal hCG slope rise, close conservative observation is warranted before any therapeutic intervention.

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