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Live Delivery Despite Abnormal Serial Rise in Serum Beta Human Chorionic Gonadotropin Levels and Sac Size Crown-Rump Length Discrepancy

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ABSTRACT

There are several parameters that when inadequate, e.g., low serum progesterone (P), low serum estradiol (E2), or a sac size crown-rump length discrepancy with a sac size lagging behind by more than one week, are poor prognostic parameters for the delivery of a healthy baby. Perhaps the most important abnormal prognostic parameter is an inappropriate rise in serial beta human chorionic gonadotropin (hCG) levels. A case is described who had abnormalities in all these parameters including, in addition, issues with both increased and decreased fetal heart rates. She did however deliver a healthy baby just three weeks before her due date. Her treatment consisted of aggressive P supplementation, plus estrogen, antibiotics, and dextroamphetamine sulfate. One cannot say for certainty whether any or all of these treatments were responsible for her good outcome. This case may be, based on the lack of rise of beta hCG levels, to be the case with the worst prognosis to deliver a live baby published to date, based on failure to have an appropriate type of rise of serial beta hCG levels.

Keywords

Antibodies, First trimester, Poor prognosis, Progesterone, Sympathomimetic amines.

Introduction

In a normal pregnancy the serum human chorionic gonadotropin (hCG) level doubles most often every two days, but in a minority of cases every three days [1-3]. Slow rising serial beta-hCG levels are usually indicative of a possible ectopic pregnancy or a poor intrauterine pregnancy with high likelihood of miscarriage [4-9]. One study found that in 22 pregnancies with slow rising beta-hCG levels, that interestingly 16 (72.7%) showed viability 6 weeks from conception, but none were viable after the first trimester [10]. However, there have been some exceptions where a live baby outcome is found despite a slow rising beta-hCG levels [11,12]. Serum progesterone (P) levels <15 ng/mL during the first trimester has been reported to be a very poor prognostic sign that could also suggest an ectopic pregnancy [13,14]. Even where there is an intrauterine pregnancy observed, a live delivered baby is rare in women not treated [13,14]. However, very aggressive P therapy has resulted in live delivery rates of 70% in women with serum P <15 ng/mL and 60% in women with serum P <8 ng/mL [15,16]. Another poor prognostic sign for an intrauterine pregnancy is a sac crown rump length (CRL) discrepancy where the sac is more than one week smaller than the CRL [17-19]. Finally, low first trimester serum estradiol (E2) levels have also been associated with a poor prognosis with intrauterine pregnancies even when there is maintenance of normal serum P levels [20-22]. A case is presented who delivered a live baby who had to date the worst serial rise in the beta-hCG level. Furthermore, she also demonstrated all the other poor prognostic signs, i.e., low serum P, low serum E2, and a sac CRL discrepancy. The report will discuss the various treatments that were rendered which may have been responsible for her good outcome.

Case Report

A 34-year-old woman had a successful vaginal delivery. Her second pregnancy occurred after 3 months of unprotected intercourse but had a miscarriage at 4 months. Her third pregnancy took 10 months of unprotected intercourse. Her first beta-hCG level was 1458 mIU/mL. Two days later the beta-hCG only increased to 1534 mIU/mL (generally indicative of either an ectopic pregnancy or an

intrauterine pregnancy that will eventually end in fetal demise or a blighted ovum, as happened in her second pregnancy). Two days later, she was spotting which turned into overt bleeding. A repeat beta-hCG was only 3273 (the level should have increased 2.5 times higher than the last one). She consulted our group the next day. Her P level was only 14.2. The presumptive diagnosis was still ectopic pregnancy vs. non-viable intrauterine pregnancy. One week from her 3273 mIU/mL level for beta-hCG, she repeated the beta-hCG level, which was now 11,136 mIU/mL. Her initial beta-hCG level taken on 5/13/20 was 1458 mIU/mL, which was consistent with her being about 22 days from conception. The level of 11,136 obtained on 5/27/20 would be consistent with a woman about 28-29 days from conception. Therefore, she would be a week behind expected. She was treated with aggressive P support at this time (100mg IM, 800mg vaginal and 200mg oral). One week later, she had an ultrasound, which showed a gestational sac measuring 18mm (consistent with 6.66 weeks) (4.66 weeks from conception) and a CRL of 16mm consistent with 7.9 weeks (5.9 weeks from conception). Subsequently, ultrasound was performed on 6-3-20. Her 11,136 beta-hCG level was taken on 5-27-20. However, from her first beta hCG level of 1458 taken on 5-13-20 she should have been 22 days from conception. Thus, by that first level, her CRL should have been consistent with 6 weeks from conception, and it was exactly what should have been expected. Furthermore, the fetal heart rate was good at 165 beats/minute. Despite some possible optimism based on the CRL size and heart rate, the sac size was a week too small, which in itself is a bad prognostic sign [19]. We decided based on this to add azithromycin in case of infection with leakage of fluid from the gestational sac which anecdotally (but unreported) has demonstrated improved survival when used by our group. Another poor prognostic sign was a low serum E2 of only 54 pg/mL at 5 weeks from conception [22].

Empirically estradiol 2mg/day was added to her treatment. Since slow rising beta hCG levels are associated with a very poor prognosis despite demonstration of fetal viability by ultrasound, that coupled with the small for dates gestational sac, and low serum E2, the patient was advised that we were still not optimistic about her chances of a live delivery, but still encouraged her to continue the medication since we had seen some exceptions to the general rule [10,12,23]. Repeat sonography was performed one week later on 6-10-20. The CRL increased to 22mm consistent with 8.67 weeks (6.67 weeks from conception) and showed appropriate growth. However, the sac size not only remained behind (18mm consistent with 7.0 weeks, 5.0 weeks from conception), but actually lost a half of week). The yolk sac measured 4x4x4mm. Fetal distress was considered with a fetal heart rate of 196 beats/minute. She also complained of pelvic cramps, and bleeding and two sub chorionic hematomas were noted measuring 16x4x18mm and 24x8x27mm). At this time point based on trying to correct a possible issue of excessive inflammation leading to immune "attack" of the fetal placental unit, dextroamphetamine sulfate was added at 30mg/day to release dopamine to decrease cellular permeability [24-26]. Repeat transvaginal sonography one week later on 6-17-20 showed the CRL increased to 32mm consistent with 7.9 weeks from conception (appropriate growth) and the sac size increased to 34mm consistent with an increase of 1.4 weeks.

The fetal heart rate decreased to 180 betas/minute. The bleeding stopped but one hematoma remained. One week later on 6-24-20, we were concerned that the sac did not increase in size at all (34mm consistent with 6.4 weeks from conception) and the CRL increased but to only 37mm consistent with 8.4 weeks from conception. The fetal heart rate was 169. The hematoma remained stable measuring 24x7x20mm with internal echoes. There was concern about the status of the pregnancy so antibiotics, aggressive P therapy (vaginal and IM) and estradiol were continued along with dextroamphetamine sulfate. Repeat sonography one week later showed a decreased fetal heart rate of 123. However, the CRL increased in size appropriately (46mm consistent with 9.28 weeks), but the gestational sac grew to 46mm consistent with 8 weeks from conception, so it increased by 10 days in one week. Her last ultrasound in our reproductive center one week later on 7-8-20 showed the fetal heart rate at 161. The sub chorionic hematoma was no longer present. She remained on the P therapy and dextroamphetamine sulfate until delivery. The antibiotic was stopped after 12 weeks from conception. She delivered 3 weeks early, but the neonate was healthy. It was subsequently determined that the baby had a bicuspid aortic valve, but no corrective surgery is being considered at this time.

Discussion

There have been many studies touting the beneficial effect of P therapy to prevent miscarriage [27]. One hypothesized mechanism is that one of its main actions to prevent fetal loss is that it stimulates the production by fetal placental cells (embryonic cells, mesenchymal cells and trophoblast cells) of the immunosuppressive protein known as the progesterone induced blocking factor (PIBF) into the fetal microenvironment which leads to suppression of natural killer (NK) cell cytolysis and a shift from thymic helper (TH)-1 cytokines to TH-2 cytokines [28]. As very common in all aspects of medicine, nothing ever seems to have unanimous acceptance of efficacy of a given treatment, which has been summarized [29]. However, the beneficial effect of P to prevent miscarriage was called into question in 2015 by the largest prospective randomized study that was even multi-centered that did not find any beneficial effect of P therapy to prevent miscarriage [30]. Nevertheless, the conclusions reached by the randomized study from Coomarasamy et al. were questionable because of improper design, i.e., not starting the P after ovulation rather than no sooner than the first positive serum beta hCG level and as late as two weeks after pregnancy was confirmed [29]. Subsequently another study by Stephenson et al using the P therapy at the right starting time once again confirmed the efficacy of using P to prevent miscarriage [31].

However, in the patient reported here the P was started late. The authors still believe that the P therapy was an essential part of her delivering a live fetus. The authors reconcile that belief by using P much more aggressively (injections plus vaginal vs. much less

P used by Coomarasamy et al). The antibiotic therapy was aimed at the possibility of an ureaplasma infection causing amniotic fluid leak leading to a small sac. However, one cannot state whether the use of azithromycin played a role in the successful outcome.

The association of low serum E2 and miscarriage could be related to early placental damage leading to low E2 levels in which case adding estrogen would not help, and thus the low E2 would merely serve as a bad prognostic sign. However, there is the possibility that it represents a defective corpus luteum of pregnancy and the possibility exists that estrogen does play some role in establishing a healthy pregnancy in the first trimester. Thus, the authors cannot say with certainty whether the addition of estradiol did or did not aid in producing this good outcome. One hypothesis contends that the postovulatory inflammatory process, which causes the predominant leukocyte in the fetal microenvironment to be a NK cell (70%), occurs because P inhibits dopamine, a biogenic amine that decreases cellular permeability [32]. By allowing increased permeability, irritants infuse into the uterine tissue causing an inflammation, which is generally not associated with pain. These NK cells are needed to remodel the thick-walled uterine arteries to create thin-walled spiral arteries needed for nutrient exchange between mother and fetus. These NK cells would attack the fetal semi-allograft were it not for secretion of PIBF which inhibits their cytolytic activity by inhibiting perforin degranulation and granzymes [26,33].

Anecdotal reports suggest that the use of drugs, e.g., dextroamphetamine sulfate, which release more dopamine from sympathetic nerve fibers can reduce excessive inflammation (as evidenced by marked relief of pelvic pain) and thus help to prevent miscarriage [25,26]. The authors think, but cannot prove, that the use of dextroamphetamine sulfate throughout the pregnancy may have played a significant role in the successful delivery of a healthy child despite what appeared to be an extremely poor prognosis during the first trimester.

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