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Low β-hCG is associated with poor prognosis in association with an embryo with positive cardiac activity

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ABSTRACT

Seven pregnancies with positive fetal heart activity and low or very low serum β-human chorionic gonadotropin (β-hCG) levels were investigated. The gestational age by dates was between 6 weeks 3 days and 8 weeks 4 days at the time of the first ultrasound scan and β-hCG ranged between 282 and 10 000 mIU/ml of the Second International Standard. The crown–rump lengths ranged between 6 and 13 mm and heart activity was always detected. Four cases were scanned because β-hCG was lower than that expected for the gestational age; in these cases the yolk sac was present but the gestational sacs were small, with a trophoblastic ring that looked thin and subjectively seemed abnormal. The β-hCG level was measured in the other three cases, because the gestational sacs were small and had a thin trophoblastic ring. In these cases, fetal heart activity was clearly imaged. All cases were scheduled for a repeat ultrasound scan 2 weeks later.

Three cases aborted spontaneously the following week, whereas in the other four no heart activity was detected in a repeat sonogram 2 weeks later. Low serum β-hCG levels indicate a poor prognosis even when associated with an embryo with positive cardiac activity detected ultrasonographically.

INTRODUCTION

Circulation through the blood vessels of an embryo is established and the heart is pulsating by the 21st post-implantation day or at 5 weeks of gestational age, when the embryo measures 1.5 mm. This may be seen by vaginal sonography by 6 weeks of gestation[1,2]. The concept of a discriminatory zone of serum β-human chorionic gonadotropin (β-hCG) was first developed by Kadar and colleagues[3] in response to the question of at what serum β-hCG level a sac should be seen on ultrasound examination and, if it is not seen, whether the pregnancy is abnormal, has aborted or is in an ectopic location. The discriminatory zone for a gestational sac detected by transvaginal or transabdominal sonography depends to some extent on the frequency of the ultrasound probe. It is also worth mentioning that the β-hCG level is measured in different units of measurement, and this can explain at least some of the differences among the results reported by several authors concerning this issue[4–12]. For a gestational sac, the lowest reported β-hCG discriminatory level of the Second International Standard units was that reported by Bernaschek and associates[12] and was equal to 750 mIU/ml with the use of transvaginal sonography. The β-hCG discriminatory levels for the yolk sac and the embryonic heart beat have also been determined[13–15]. The significance of low maternal serum β-hCG combined with positive fetal heart function during early pregnancy, however, has not yet been adequately investigated in the current literature[13,16]. The objective of our study was to investigate this issue.

MATERIAL AND METHODS

Seven early first-trimester pregnancies detected between November 1991 and February 1993, with positive fetal heart activity and low or very low β-hCG, were investigated. Over 500 first-trimester pregnancies were examined by the authors during the same time period. Menstrual age (time elapsed from the last menstrual period in weeks) ranged between 6 weeks 3 days and 8 weeks 4 days at the time of the first ultrasound scan. Four cases were chosen for scanning because β-hCG was lower than expected for the gestational age. These patients were neither bleeding nor in pain and the β-hCG level was measured to diagnose the pregnancy. Unexpectedly, the fetal heart activity was positive, and the gestational sacs were small, with a trophoblastic ring that looked thin and subjectively seemed abnormal (Figure 1). The yolk sac was present in all cases. Having

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observed the possibility of having very low β-hCG levels associated with a living embryo in the first group, we investigated the alternative presentation in three other cases. In these three cases, β-hCG was measured because the gestational sacs were smaller than expected, with a thin trophoblastic ring, while a fetus with positive heart activity was present. These three patients were referred for an ultrasonographic scan to diagnose the pregnancy, without any other specific indication such as bleeding or pain. Sonographic evaluation was performed transabdominally in four cases and transvaginally in the other three cases.

Quantitative serum β-hCG levels were determined by a radioimmunoassay method for the β-subunit using the Amerlex-M β-hCG RIA kit. The assays were calibrated against the Second International Standard. A maternal blood sample was taken within 24 h of the sonographic scan.

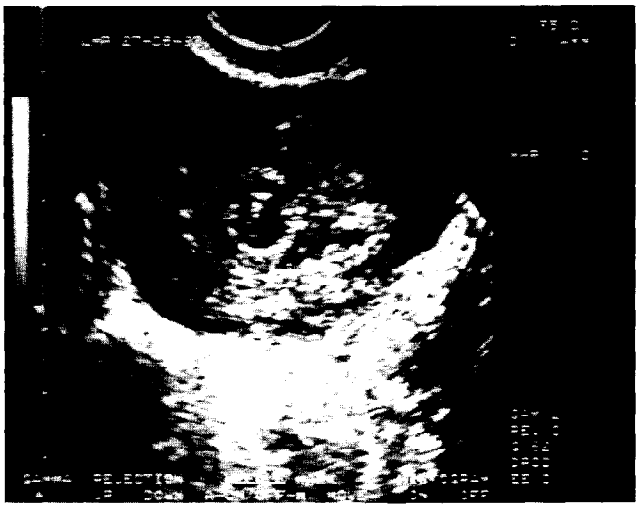

Figure 1 Scan showing small gestational sac with thin and subjectively abnormal trophoblastic ring

RESULTS

The maternal serum β-hCG levels ranged between 282 and 10 000 mIU/ml of the Second International Standard. Only one sample had a β-hCG level of 10 000 mIU/ml, whereas the other six ranged between 282 and 3700 mIU/ml. In five cases, the β-hCG level was very low, being well outside the normal range according to menstrual age, whereas in the other two, β-hCG levels were just above the lower limit of the normal range (cases 5 and 6). Clinical and ultrasonographic findings in relation to β-hCG level and pregnancy outcome are presented in Table 1.

Mean values for gestational sacs and crown–rump length according to menstrual age are derived from the combined data of Robinson and Hadlock[17]. The crown–rump length ranged between 6 and 13 mm in the first sonogram, when fetal heart function was positive. In cases 1 and 7, the crown–rump length was abnormally low whereas in the rest of the cases, crown–rump length measurements were within normal limits. The size of the gestational sac was smaller than expected according to menstrual age in four cases and within normal limits in three cases. Fetal heart rates were not recorded.

Three cases aborted spontaneously within a week from the first scan, whereas in the other four cases no heart function was detected in a repeat sonogram two weeks later.

DISCUSSION

As pregnancy progresses, the volume of trophoblastic tissue increases, leading to an increase in the production of β-hCG. At the same time, the sac and the embryo are growing in size. Once the sac becomes large enough, it will become visible during an ultrasound examination. Once the sac diameter reaches a certain point, it will be consistently detected by an examiner. The maternal serum β-hCG level corresponding to this particular size

Table 1 Clinical and ultrasonographic findings in relation to β-hCG levels and outcome. Mean values and ranges are shown in parentheses

Case	*Menstrual age* (weeks + days)	*Ultrasound*	*Crown–rump length* (mm)	*Gestational sac* (mm)	*Yolk sac* (mm)	*Measured β-hCG* (mIU/ml)	*Mean, range β-hCG concentration* (mIU/ml 2nd IS)	*Outcome*
1	7 + 5	TV	6 (14)	7 (24)	3	1000	29 800 (10 000–73 700)	spontaneous abortion 7 days later
2	7 + 3	TA	10 (12)	17 (22)	4	800	29 800 (10 000–73 700)	embryonic demise 14 days later
3*	8 + 0	TA	13 (16)	19 (26)	4	2500	46 100 (17 500–93 900)	embryonic demise 14 days later
4	6 + 5	TA	13 (8)	20 (18)	4	282	14 900 (2 600–50 200)	spontaneous abortion 4 days later
5*	6 + 3	TV	7 (6)	9 (16)	3	2950	14 900 (2 600–50 200)	spontaneous abortion 6 days later
6	6 + 3	TA	7 (6)	10 (16)	3	3700	14 900 (2 600–50 200)	embryonic demise 14 days later
7*	8 + 4	TV	9 (20)	12 (30)	3	10 000	46 100 (17 500–93 900)	embryonic demise 12 days later

TA, transabdominal; TV, transvaginal; *, expected according to menstrual age; †, cases in which β-hCG was examined secondarily to ultrasonographic findings

is known as the discriminatory zone value for a specific ultrasound probe[3-5].

This can also be viewed from a different perspective. The level of β-hCG is a quantitative marker of the function of the trophoblast. The living embryo, with positive heart activity that can be detected by ultrasound, has to have a minimum trophoblastic function, below which it is not possible to survive. One could expect to have an intermediate zone where survival of the fetus could be possible despite low trophoblastic activity, a third zone where trophoblastic function could be adequate for all fetuses and a fourth where β-hCG production is abnormally high, as it is in trophoblastic disease.

Several sonographic signs have already been recognized as risk factors for subsequent embryonic or fetal demise. Embryonic bradycardia is considered a poor prognostic finding during early pregnancy[18,19]. Unfortunately, the embryonic heart rate in our cases was not estimated. Discrepancy between the size of the embryo and stated menstrual age also increases the risk of subsequent demise[20]. This kind of discrepancy was found in at least two of our cases. First-trimester oligohydramnios, seen as a small gestational sac relative to the size of the embryo, is frequently associated with subsequent demise[21]. Bromley and associates[22] reported that a gestational sac diameter less than 4 mm larger than the crown–rump length was universally associated with pregnancy failure. This finding was detected in four of our cases, as shown in Table 1.

Thus the results of our study are in agreement with those of others on first-trimester pregnancies but, more than that, we believe that they add some original observations. Our findings indicate that a fetus with a crown–rump length of 13 mm can have positive heart function with a maternal serum β-hCG level as low as 282 mIU/ml. On the other hand, crown–rump length values of 6–13 mm combined with β-hCG of 282–10 000 mIU/ml (mean 3033 mIU/ml) in association with positive cardiac activity are expected to have an unfavorable outcome over the coming weeks. This information may be helpful in counselling every woman who demonstrates a living embryo and in the management of the specific pregnancy as well. The finding of an abnormally low β-hCG level may also be helpful for the investigation of the pathophysiology and etiology of abortion. Abnormal implantation and placentation seem to be reasonable pathophysiological mechanisms that might explain not only the low values of β-hCG but also the unfavorable outcome of these cases. The cause of this abnormally low trophoblastic function is either a low potential of the conceptus or a hostile uterine environment.

The assessment of early pregnancy by transvaginal color Doppler ultrasonography[23] may be very helpful for the investigation of such cases. In a recent case of a living embryo with crown–rump length of 8 mm, mean gestational sac of diameter 12 mm and β-hCG level of 860 mIU/ml that we studied with transvaginal color Doppler, the resistance indices of peritrophoblastic flow and uterine artery flow were within normal limits according to the published findings of Kurjak and colleagues[23]. A repeat ultrasonographic scan a week later revealed embryonic demise. This suggests that an intrinsically low growth potential of the conceptus must be considered responsible for the final pregnancy failure in at least some of these unfavorable pregnancies, and that abnormal presentation is not always the cause.

In conclusion, a low β-hCG level indicates an unfavorable outcome for the early pregnancy in which fetal heart function is also detected by real-time sonography. Although ultrasonographic detection of fetal heart function in early pregnancy has been considered a good prognostic factor, this seems not to be the case when it is combined with a low maternal serum β-hCG level. Further investigation is still necessary, however, since the number of pregnancies studied is small.

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