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ORIGINAL ARTICLE

Perinatal outcome of fetuses with high (>4.0 MoMs) first-trimester free beta-hCG levels

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ABSTRACT

Objective: To analyze the perinatal outcome of fetuses with high first-trimester free beta human chorionic gonadotrophin (b-hCG) levels and compare it with controls.

Method: Prospectively collected data from 113 fetuses with free b-hCG levels >4.0 MoMs and 3176 controls were analyzed to compare the rates of chromosomal abnormalities, structural defects, preeclampsia, hypertension, abruption, miscarriage, low birthweight, intrauterine or neonatal death, gestational diabetes and NICU admissions. Odds ratios with 95% confidence intervals (CIs) were calculated.

Results: Fetuses with free b-hCG levels >4.0 MoMs had a 8.8% (95% CI 4.8-15.3) rate of chromosomal abnormalities, mostly Down syndrome. The prevalence of preeclampsia in this group was 3.8% (95% CI 1.5-9.5), significantly higher (OR 3.1, 95% CI 1.1-8.9) compared to controls. There were no significant differences in any of the other outcomes. There were no cases of intrauterine or neonatal death.

Conclusion: The main concern in fetuses with high first-trimester free b-hCG levels is increased risk for chromosomal abnormalities. Fetuses with a normal karyotype may be at increased risk for preeclampsia.

KEY WORDS Chorionic gonadotrophine, growth, preeclampsia, PAPP-A

Introduction

The levels of maternal serum free beta chorionic gonadotrophin (free beta-hCG) and pregnancy associated plasma protein –A (PAPP-A) have been measured for over a decade in the context of first-trimester screening for chromosomal abnormalities, and specific level

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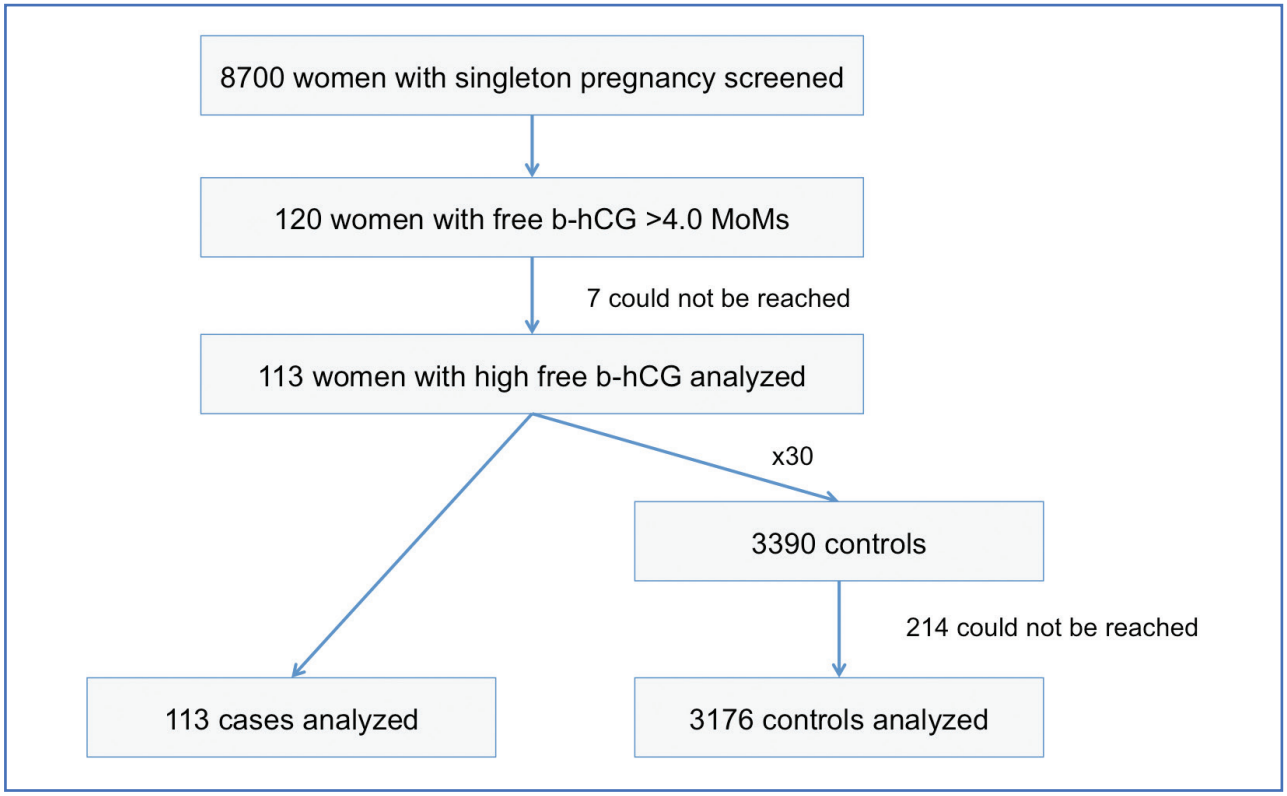

Figure 1. *Flow chart of participant selection*

patterns have been recognized for different conditions. Thus, compared with normal foetuses, those with trisomy 21 tend to have higher levels of free beta hCG (median: 1.95 MoMs) and lower levels of PAPP-A (median: 0.437 MoMs) [1], those with trisomies 18 and 13 tend to have lower levels of both hormones (median free beta hCG: 0.2 and 0.5 MoMs, respectively; median PAPP-A: 0.2 and 0.3 MoMs, respectively [2], and foetuses with triploidy tend to have significantly increased levels of free beta hCG (median 4.59 MoMs) and significantly low levels of PAPP-A (median 0.12 MoMs) [3].

Furthermore, as both proteins are produced by the trophoblast and their secretion may be altered in placenta-related obstetric complications, their levels have been studied as predictors for conditions such as pre-eclampsia (normal free beta hCG, low [median 0.844 MoMs] PAPP-A) [4], fetal growth restriction (normal free beta hCG, low [median 0.813 MoMs] PAPP-A) [4], small for gestational age (SGA) foetuses (normal free beta hCG, low [median 0.76 MoMs] PAPP-A) [5] and fetal death (low levels increase the risk) [6].

Approximately 1% of women will have free beta hCG levels ≥3.914 MoMs. Total beta hCG levels >4.0 MoMs have been associated with high risk for spontaneous miscarriage, small-for-gestational-age infants, pregnancy-associated hypertensive disorder, and preterm delivery in the second trimester [7], and 5 out of 6 fetuses with extremely high (>15 MoMs) hCG levels had pregnancy complications in a small series from Israel [8].

The aim of this study was to record the perinatal outcome of pregnancies with increased (>4.0 MoMs) first-trimester levels of free beta hCG and compare it with the outcome of pregnancies with lower (≤4.0 MoMs) free beta hCG levels.

Methods

This is a study of prospectively collected data from singleton pregnancies, drawn from a population attending routine first-trimester screening for aneuploidies in two prenatal diagnostic centers in Greece within three years. The study was approved by the corresponding Ethics Committees and consent was obtained from all participants.

All fetuses were scanned between 11+0 – 13+6 weeks by two Fetal Medicine Foundation (FMF) –accredited operators (ME and AS) according to the FMF protocol

Table 1. Descriptive data for cases with free b-hCG levels >4.0 MoMs (N=113) and controls (N=3176)

	Cases (≥4.0 MoMs)	Controls (<4.0 MoMs)	p-value
Median free bhCG MoMs	4.96	0.98	0.0001
Median PAPP-A MoMs	1.13	0.98	0.01
Median risk for trisomy 21	1:1478	1:9558	0.0001
Mean CRL (mm) (SD)	61.6 (7.0)	60.8 (6.8)	0.015
Mean NT (SD)	1.7 (0.4)	1.7 (0.4)	0.06
Mean gestational age at birth (wks) (SD)	38.5 (2.0)	39.0 (1.5)	0.06
Mean birth weight (gr) (SD)	3136 (626)	3230 (458)	0.094
Mean maternal age (yrs) (SD)	33.3 (5.2)	31.7 (4.2)	0.0001
Mean maternal BMI (SD)	23.8 (4.6)	24.4 (6.8)	0.546
Fetal sex (%male/female)	42.3/56.7	52.3/47.7	0.0001

(www.fetalmedicine.com). All scans were performed transabdominally, using either a GE E6 Expert or a GE E8 Expert ultrasound machine (wide band convex volume probe, 2.0-8.0 MHz, GE Medical Systems Kretztechnik, GmbH & Co., OHG, Austria). The data were entered into a specialized fetal database software (Astraia Obstetrics, Astraia Software GmBH, Munich, Germany).

Maternal serum free beta hCG and PAPP-A were measured using either a Brahms Kryptor (Kryptor system, Brahms AG, Berlin, Germany) or a Roche Elecsys (Roche Diagnostics Ltd., Switzerland) analyzer. The measured concentrations of the two hormone were converted to MoMs corrected for fetal crown–rump length (CRL), maternal weight, smoking status, racial origin, parity and method of conception according to the FMF software as described before [9].

Recorded outcome measures included pregnancy outcome (live birth, termination, miscarriage, intrauterine death / stillbirth, perinatal death), fetal karyotype, presence of major fetal structural abnormalities, preeclampsia, fetal growth restriction (defined as birth weight ≤5th centile for our screening population), cholestasis, placental abruption, gestational diabetes mellitus and admission to the neonatal intensive care unit (NICU).

In order to identify infants with birth weight below the fifth centile of our population, we first constructed normal ranges were constructed for birth weight, separately for boys and girls, as described according to Royston and Wright [10]. The birth weight for boys was described by the equation:

$Log_{10}BW= -0.342952 +0.174748*GA -0.001943*GA^2$ (SD=0.049678).

The corresponding equation for girls was:

$Log_{10}BW= -0.898371 +0.203513*GA -0.002327*GA^2$ (SD= 0.258046 -0.005390*GA)

For each woman with free beta hCG levels ≥4.0 MoMs, the next thirty women in the database with levels <4.0 MoMs were used as controls. Women were contacted by phone at least 4 months after their expected delivery date. When a woman could not be reached after two attempts, she was replaced by the next in list. Comparisons between the two groups were made using the chi-square (χ^2) or Fisher test, and the odds ratios with their respective confidence intervals (CIs) were calculated (IBM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp).

Results

The flowchart of participants is illustrated in Figure 1. One hundred and twenty women with a singleton pregnancy had free b-hCG levels ≥4.0 MoMs at 11^{+0} – 13^{+6} weeks (1.4%) . Seven of them were lost to follow-up and therefore the analysis included 113 women with free bhCG levels ≥4.0 MoMs and 3176 controls. The descriptive data for the two groups are shown in Table 1. The proportion of female foetuses was higher in cases

Table 2. Outcomes of cases with free b-hCG levels >4.0 MoMs (N=113) and controls (N=3176)

	Cases n/N (%)	Controls n/N (%)	OR (95% CI)
Live birth	103/113 (91.2)	3077/3176 (96.9)	0.3 (0.2-0.7)
Miscarriage	0	25/3176 (0.8)	N/A
Termination of pregnancy	10*/113 (8.8)	56*/3176 (1.8)	5.4 (2.7-10.9)
Intrauterine death	0	14/3176 (0.4)	N/A
Neonatal death	0	4 (0.1)	N/A
Preeclampsia	4/104 (3.8)	39/3095 (1.3)	3.1 (1.1-8.9)
Gestational hypertension	1/103 (1.0)	13/3096 (0.4)	2.3 (0.3-17.9)
Gestational diabetes mellitus	1/103 (1.0)	34/3095 (1.1)	0.9 (0.1-6.5)
Placental abruption	0	5/3095 (0.2)	N/A
Birth weight <5th centile	6/101 (5.9)	174/3011 (5.8)	1.0 (0.4-2.4)

with free b-hCG levels >4.0 MoMs (56.7%) than controls (47.7%) (p<0.001).

The distribution of outcomes in the two groups is shown in Table 2. Fetuses with free b-hCG levels >4.0 MoMs had significantly higher odds for termination of pregnancy because of chromosomal or structural abnormalities (OR 5.4, 95% CI 2.7-10.9). The rate of chromosomal abnormalities was 8.8% (95% CI 4.8-15.3); one fetus had triploidy (12.360 MoMs), eight had trisomy 21 (4.422-7.111 MoMs) and one had Turner syndrome (4.049 MoMs). The estimated risk for trisomy 21 for the eight affected cases ranged form 1:2 to 1:59 at the combined first-trimester screening. The risk for preeclampsia was also increased in cases with free b-hCG levels >4.0 MoMs (OR 3.1, 95% CI 1.1-8.9), while no significant difference was found in the other outcomes studied. All four cases with preeclampsia in the high b-hCG group were found in women with levels >5.0 MoMs (4/51 or 8%).

Discussion

In this case-control study, we found that free b-hCG levels >4.0 MoMs were associated with approximately 9% for chromosomal abnormalities, mostly Down syndrome, and 4% risk for preeclampsia. The risk for other placenta-related complications, including fetal growth restriction, was not found to significantly differ between the two groups.

Free beta-hCG levels >4.0 MoMs approximately correspond to the highest 1% of the measurements[9]; 1.3% of our population were found to have such levels. Since Down syndrome is characterized by high free b-hCG levels, women with such levels are commonly given the option for invasive prenatal diagnosis. Indeed, 25% of these fetuses had risk for Down syndrome >1:250, 20% had risk >1:100 and 7% actually had trisomy 21. We further analyzed the outcome of these fetuses in order to optimize counseling for this selected population.

We found that women with free b-hCG levels >4.0 MoMs had three times higher risk for preeclampsia compared to controls. Notably, all our cases with high free-hCG and preeclampsia had normal PAPP-A levels, ranging from 0.854 to 1.912.Maternal serum b-hCG concentrations have been tried as predictors for preeclampsia in the settings of both first- and second-trimester screening. The results are conflicting, as both lower [11], unchanged [12] or higher [13] free b-hCG levels have been reported in women who subsequently developed preeclampsia as opposed to controls, whereas free b-hCG was not found to be a significant factor in multivariable prediction models [14, 15]. In a recent study, *total* hCG levels ≥90th centile in nulliparous or≥ 95th centile in multiparous) were associated with a more than threefold risk for early-onset severe preeclampsia [16].

Second-trimester b-hCG levels >4 MoMs have been associated with a non-significant trend towards increased risk for low birth weight and hypertensive disease of

pregnancy [17]. There is a theoretical basis for both reduced and increased b-hCG levels in preeclampsia. Women developing preeclampsia were found to have increased (and correlated) hydrogen peroxide and hCG levels, indicating that hCG may be a marker of oxidative stress [18]; moreover, a study in cultured trophoblastic cells showed that b-hCG secretion in response to hydrogen peroxide stimulation follows a bimodal pattern, with low stimulation enhancing and high stimulation suppressing cytotrophoblastic hCG secretion [19]. The dual pattern has also been reported for the soluble LH/hCG receptor (sLHCGR); most of the pregnancies developing preeclampsia exhibit very low levels, probably indicating early placental failure, whereas a significant proportion of such pregnancies have very high sLHCGR levels, probably associated with reduced hCG bioactivity and abnormal endothelial and immune response [20]. The dual pattern may, at least partly, explain the lack of significance of free b-hCG in regression models, where it is used as a continuous variable. Notably, none of the women with free b-hCG <0.3 MoMs (which roughly corresponds to the first centile in our population) and 0.7% of those with levels <0.4 MoMs (5th centile in our population) developed preeclampsia. Two out of the four preeclampsia cases in women with free b-hCG levels >4.0 MoMs resulted in delivery before 34 weeks, however much greater numbers of cases with increased free b-hCG are needed in order to draw firm conclusions.

Sharony et al. analysed the outcome of pregnancies with extremely high (>15 MoMs) free b-hCG levels, which had a frequency of about 1:8000 in their population. In 5 out of their 6 cases, an obstetric complication (intrauterine death, prematurity, failure to thrive) developed, without any apparent diagnosis responsible for that, except from one case with hydatidiform mole with a coexisting normal fetus [8]. Notably, the case with the highest free b-hCG level (12.360 MoMs) in our series was also a triploid fetus, and the patient developed preeclampsia at 17 weeks secondary to the development of theca lutein cysts.

Apart from chromosomal abnormalities and an association with preeclampsia, we did not detect an association of high free b-hCG levels with (or a trend towards) other obstetric or fetal complications. Similarly, in their prospective study, Brameld et al. concluded that high (>4.1 MoMs) levels of free b-hCG have limited use as predictors for adverse pregnancy outcomes [21]. Still, the rarity of certain events (e.g perinatal death) would require a much larger pool of cases, and therefore a 100-fold larger screening population, in order for potential associations to reach significance.

Conclusion

The data from our series indicate that, after excluding chromosomal abnormalities, a moderately increased risk for preeclampsia may be a concern in women with increased free b-hCG levels. Larger datasets are needed in order to substantiate this effect and determine whether these women would benefit from modified pregnancy management. ■

Conflict of interest: None

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