The Relationship between Perinatal Outcome of Singleton Pregnancies and Isolated Highly Elevated Levels of Maternal Serum Human Chorionic Gonadotropin at Mid-Gestation

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Abstract

Background: The measurement of maternal serum human chorionic gonadotropin as a predictor of fetuses with Down syndrome has been in use since 1987.

Objectives: To determine the correlation between extremely high levels of hCG at mid-gestation and maternal and fetal complications.

Methods: The study group consisted of 75 pregnant women with isolated high levels of hCG (> 4 MOM) at mid-gestation, and the control group comprised 75 randomly selected women with normal hCG levels (as well as normal alpha-fetoprotein and unconjugated estriol levels). In addition to demographic information, we collected data on fetal anomalies, chromosomal aberrations, pregnancy complications, and results of neonatal tests.

Results: There was a significant increase in the frequency of fetal anomalies (detected by ultrasound), low birth weight and neonatal complications in the study group. We also found an increased rate of fetal/neonatal loss proportional to the increasing levels of hCG (up to 30% in levels exceeding 7 MOM).

Conclusion: Our study demonstrated an increased frequency of obstetric complications that was closely associated with high hCG levels. The study also raises questions about the accuracy of the Down syndrome probability equation in the presence of extremely high levels of hCG where data on the frequency of Down syndrome are severely limited.

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In 1987 the use of maternal serum human chorionic gonadotropin as a predictor of pregnancies of fetuses with Down syndrome was established [1]. A year later, the first study using the triple test (maternal serum levels of hCG, alpha-fetoprotein, and unconjugated estriol) as a reliable method for predicting the probability of Down syndrome was published [2]. The authors demonstrated that the mean hCG levels in pregnancies of fetuses with Down syndrome was 2.04 MOM. The distribution of Down syndrome according to hCG levels was Gaussian, with only 10% of cases having an hCG level greater than 4.13 MOM.

In 1992, a non-genetic complication occurring in pregnant women with an elevated hCG level was reported [3]. The authors described a woman in her 16th week of pregnancy with an hCG level of 9.62 MOM who later developed a fulminant toxemia accompanied by HELLP (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets syndrome). This report was the first among many to point out the correlation between high levels of hCG and various complications of pregnancy. As reported in numerous studies [3-14], elevated mid-trimester hCG is correlated with an increasing incidence of intrauterine growth retardation, intrauterine fetal death, low birth weight, and pregnancy-induced hypotension. All except two of the studies used as an inclusion criterion an hCG level of 2–3 MOM, while the data on pregnancy outcome associated with hCG levels greater than 4 MOM are limited to two reports – one with 29 women [11] and the other with 49 women [15].

The aim of our study was to expand our knowledge and investigate further the relationship between isolated maternal serum hCG levels greater than 4 MOM at 16–18 weeks of gestation and perinatal outcome (fetal anomalies, chromosomal aberrations, pregnancy complicationsm, neonatal results) in singleton pregnancies and to try to define trends in their occurrence according to rising levels of hCG.

Patients and Methods

This study was carried out between 1994 and 1998 in the Department of Medical Genetics at the Rabin Medical Center, Petah Tikva, Israel, and was approved by its Institutional Review Board. Our inclusion criteria were women in the second trimester of a singleton pregnancy with elevated hCG levels (greater than 4 MOM) and normal levels of alpha-fetoprotein and unconjugated estriol. Ninety women were eligible for inclusion but 15 were lost to follow-up, leaving 75 women in the study group.

Each woman was interviewed a few months after delivery and each was asked to complete a detailed questionnaire that included questions on their general health, socioeconomic status, obstetric background, and a detailed history of complications during the recent pregnancy as indicated by elevated hCG levels.

The control group comprised 75 women selected randomly from a large pool of women who had normal hCG levels (as well as normal alpha-fetoprotein and unconjugated estriol levels) in their second-trimester biochemical test. The biochemical analysis of this group was performed in the same laboratory as that of the study group. Each woman in the control group had a singleton pregnancy and data from their pregnancies were collected in the same manner as for the study group.

hCG = human chorionic gonadotropin

The statistical analysis was performed using the chi-square test for discrete variables and the Student *t*-test for non-discrete variables. The analysis was carried out on two levels: a) comparing the results of the study group and the control group, and b) dividing the study group into three subgroups according to the hCG levels, as follows: hCG levels of 4–5 MOM (38 women), hCG levels of 5.01–7 MOM (28 women), and hCG levels greater than 7 MOM (9 women). All three subgroups were compared for each of the variables separately and in different combinations.

Results

Comparison of the study and control groups

There was no statistically significant difference between the study and the control groups regarding the mother's ethnic origin, the number of previous pregnancies, the number of abortions, the number of women for whom this was the first pregnancy, maternal age, and the medical centers where the delivery and the follow-up took place.

The mean hCG level in the study group was 5.59 MOM ± 2 (4.02–16.3 MOM), whereas in the control group the mean level was 1.1 MOM ± 0.5 (0.31–2.34 MOM). There were no significant differences in the alpha-fetoprotein and unconjugated estriol levels between the two groups.

The average combined risk for Down syndrome was 1:175 (SD 1:226) in the study group and 1:5007 (SD 1:3402) in the control group. The amniocentesis rate in the study group was 79% (59/75) and only 6.7% (5/75) in the control group. Table 1 summarizes pregnancy and neonatal complications in both groups.

Only one fetus with a chromosomal aberration (Down syndrome) was found in the study group and the pregnancy was terminated; none were found in the control group. The study group included six women with changes in the quantity of amniotic fluid (three with oligohydramnios and three with polyhydramnios), and five whose fetuses had suspected anomalies including bilateral ventriculomegaly in two cases, one case each of single kidney and neural tube defect, and a fetus with multiple anomalies who died later in the pregnancy. In the control group there was only one woman with mild polyhydramnios. The difference in the number of cesarean sections performed was not statistically significant between the study and control groups (17% vs. 14% respectively).

Neonatal complications were present in six infants in the study group compared with none in the control group. Two of the six had neonatal jaundice with bilirubin levels higher than 15 mg/dl, two had respiratory complications, one had hypoglycemia, and one had sepsis.

The mean birth weights were 3049 ± 697 and 3253 ± 540 g in the study and control groups respectively ($P < 0.05$). Of the newborns in the study group, 17.6% were born with a birth weight of less than 2500 g, compared with only 7% in the control group ($P < 0.05$).

Table 1. Demographic parameters, pregnancy complications and neonatal outcome of the study and control groups

	Study group (n=75)	Control group (n=75)	Relative risk	*P*
First pregnancy	28/74 (37.8%)	21/75 (28%)	1.35	NS
Spontaneous pregnancy	64/75 (85.3%)	71/75 (94.6%)	0.90	NS
Induction of ovulation	4/75 (5.3%)	3/75 (4%)	1.33	NS
In vitro fertilization	7/75 (9.3%)	1/75 (1.33%)	7	NS
Fetal anomalies	5/75 (6.7%)	1/75 (1.33%)	5	NS
Polyhydramnios	3/75 (4%)	1/75 (1.33%)	3	NS
Oligohydramnios	3/75 (4%)	0 (0%)	–	NS
Preeclampsia	5/75 (6.7%)	3/75 (4%)	1.67	NS
Diabetes	2/75 (2.7%)	0 (0%)	–	NS
Premature contractions	11/75 (14.7%)	9/75 (12%)	1.22	NS
Bleeding	12/75 (16%)	14/74 (18.9%)	0.84	NS
Placental abruption	0 (0%)	2/75 (2.7%)	–	NS
Premature rupture of membranes	3/75 (4%)	2/75 (2.7%)	1.5	NS
Preterm delivery < 37 week	11/71 (15.5%)	5/72 (6.94%)	2.23	NS
Week of delivery (mean ± SD)	38.85 ± 2.54	39.7 ± 2	–	NS
Males/females	34/36	40/32	–	NS
Birth weight (g ± SD)	3041 ± 697	3253 ± 540	–	0.048
Birth weight < 2500 g	12/68 (17.6%)	5/72 (6.94%)	2.5	0.04
Small for gestational age	6/68 (8.82%)	3/75 (4%)	2.11	NS
Neonatal complications	6/75 (8%)	0 (0%)	–	0.02
Intrauterine fetal loss	5/75 (6.7%)	3/75 (4%)	1.66	NS
Neonatal loss	2/75 (2.7%)	0 (0%)	–	NS
Alive and well	68/75 (90.7%)	72/75 (96%)	0.94	NS

NS = not significant

Table 2. Demographic parameters, pregnancy complications and neonatal outcome according to hCG levels

Parameter	Control group (n=75)	4-5 MOM (n=38)	5-7 MOM (n=28)	> 7 MOM (n=9)	*P*
First pregnancy	21/75 (28%)	15/38 (39.5%)	11/27 (40.7%)	2/9 (22.2%)	0.55
Fertility treatment	4/75 (5.3%)	4/38 (10.5%)	6/27 (22.2%)	1/9 (11.1%)	0.27
Fetal anomalies	1/75 (1.3%)	4/38 (10.5%)	1/26 (3.8%)	0 (0%)	NS
Polyhydramnios	1/75 (1.3%)	1/38 (2.6%)	2/26 (7.7%)	0 (0%)	0.48
Oligohydramnios	0 (0%)	2/38 (5.2%)	1/26 (3.8%)	0 (0%)	0.77
Preeclampsia	3/75 (4%)	2/38 (5.2%)	2/26 (7.7%)	1/9 (11.1%)	0.80
Diabetes	0 (0%)	2/38 (5.2%)	0 (0%)	0 (0%)	0.39
Premature contraction	9/75 (12%)	10/38 (26.3%)	1/26 (3.8%)	0 (0%)	0.02
Bleeding	14/74 (18.9%)	7/38 (18.4%)	2/26 (7.7%)	3/9 (33.3%)	0.18
Premature rupture of membranes	2/75 (2.6%)	3/38 (7.9%)	0 (0%)	0 (0%)	0.24
Amniocentesis	5/75 (6.6%)	30/38 (78.9%)	21/27 (77.7%)	8/9 (88.8%)	0.95
Preterm delivery < 37 weeks	5/72 (6.9%)	6/37 (16.2%)	4/27 (14.8%)	1/7 (14.2%)	NS
Cesarean section	10/72 (13.8%)	4/38 (10.5%)	6/25 (24%)	2/9 (22.2%)	NS
Males/females	40/32	17/20	13/13	4/3	0.84
Females	32/72 (44.4%)	20/37 (54%)	13/26 (50%)	3/7 (42.9%)	0.85
Birth weight < 2500 g	5/72 (6.9%)	6/38 (15.8%)	4/28 (14.3%)	2/9 (22.2%)	NS
Neonatal complications	0 (0%)	2/38 (5.2%)	3/26 (11.5%)	1/9 (11.1%)	0.17
Fetal or perinatal death	3/75 (4%)	2/38 (5.2%)	2/28 (7.1%)	3/9 (33.3%)	0.01

Correlation between hCG levels and frequency of complications

The study group was divided into three subgroups: hCG levels ranging from 4.01 to 5 MOM with a mean of 4.4 MOM in 38 women, hCG levels between 5.01 and 7 MOM with a mean of 5.8 MOM in 28 women, and hCG levels higher than 7.01 MOM with a mean of 9.9 MOM in 9 women. The three groups were similar with regard to the mother's ethnic origin, number of previous pregnancies, number of abortions, and the medical centers where the deliveries took place. The mean maternal age in the third group was 2.5 years older than the average age of the study group as a whole. Table 2 summarizes the data for the three subgroups of the study group.

The rate of intervention during labor increased with the increase in the hCG level from 12.1% in the first subgroup to 31.6% in the second and third subgroups. This difference was statistically significant ($P = 0.027$). The birth weights of the infants were 3152 ± 607 g in the first subgroup compared to 2940 ± 775 g in the other two subgroups.

The risk of fetal or neonatal loss according to the hCG levels was 4% (3/75) when the hCG level was less than 2 MOM, 9.3% (7/75) when the level was more than 4 MOM, 13.5% (5/37) when > 5 MOM, 20% (4/20) when > 6 MOM, and 33.3% (3/9) when > 7 MOM. In the control group there were three pregnancy losses (4%). One was due to premature rupture of the membranes and two were spontaneous abortions.

Regarding the study group, in the first subgroup there was a 5% fetal or postnatal mortality rate (2/38); one was a fetus with Down syndrome whose mother decided to terminate the pregnancy and the other was a child who died at the age of 3 years due to a brain tumor. In the second subgroup the rate of fetal or neonatal deaths was 7% (2/28); one was due to a neural tube defect and this pregnancy was terminated at the request of the parents, and the second died after birth from an unknown cause. In the third subgroup 33% (3/9) died; two died *in utero* and the third was born weighing only 780 g and died at the age of 3 months due to sepsis. Figure 1 summarizes the increasing risk for fetal and postnatal loss according to the rising levels of hCG.

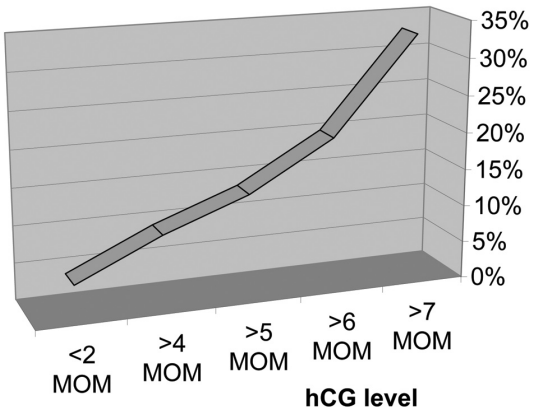

Figure 1. Frequency of perinatal mortality according to increasing levels of hCG

Discussion

Regarding the number of amniocenteses that were performed, there was a highly significant difference between the women in the study group and those in the control group. In the study group 79% of the women underwent amniocentesis, compared to only 7% of the women in the control group ($P = 0.001$). This difference underscores the value of the probability equation for the risk of Down syndrome in the mother's decision whether or not to undergo amniocentesis. Of all the biochemical markers, the hCG level in the risk equation for Down syndrome is the most highly significant and therefore its level will strongly determine whether amniocentesis will be performed. It can also be argued that the large difference in the rate of amniocentesis might bias the results of the study. However, no cases of premature rupture of the membranes, bleeding or infection were detected among the women in the study group after performing the amniocentesis. All the deaths in the study group occurred several months after the procedure.

By comparing our results with those of previous studies [3,4,6,7,10-15] [Table 3], it appears that intrauterine growth retardation, preeclampsia, preterm delivery, low birth weight, and fetal or neonatal death are the most common complications of elevated hCG, and therefore these complications should be carefully looked for in all pregnancies in this risk category. Using higher cutoff levels of hCG seems to correlate with the increasing frequency and severity of the same types of complications. Parameters whose occurrence was proportional to the increase in the hCG levels were low birth weight and fetal or postnatal death. In the subgroup with the highest hCG levels (above 7 MOM) the death rate was 33% (3/9). Two of these were lost during pregnancy and the third died

Table 3. Summary of different pregnancy complications found in previous studies and in our study according to different cutoff levels of hCG

Author of study [ref]	No. of patients	SGA (RR)	LBW (RR)	IUFD or neonatal death (RR)	PIH (RR)	Preterm deliveries (RR)
hCG levels above 2–3 MOM						
Benn et al. [4]	242	3.01		4.38		2.61
Gonen et al. [15]	284	2.8			4.4	
Liepmann et al. [6]	460	1.8	4.0			2.8
Tanaka et al. [7]	42	4.8				
Heikkila et al. [10]	37		2.11			2.08
Hershkovitz et al. [11]	121					
Heinonen et al. [14]	355	1.46	1.56			
hCG levels above 4 MOM						
Hershkovitz et al. [11]	29					
Gonen et al. [15]	49				6.8	3.3
> 4 (present study)	75	2.11	2.5	1.66	1.67	2.23
> 5 (present study)	37		2.53	3.37	2.02	1.94
> 7 (present study)	9		3.19	8.32	2.77	2.04

RR = relative risk, SGA = small for gestational age, LBW = low birth weight, IUFD = intrauterine fetal death, PIH = pregnancy-induced hypertension

due to neonatal complications. Since data on such highly elevated hCG levels are unknown, we cannot judge whether this disturbing result was accidental or not. Further information must be obtained on this unique population.

In an attempt to explain the growing propensity of pregnancy complications both in euploid and aneuploid pregnancies with elevated maternal serum hCG levels, in 1999 Liu et al. [16] compared the placentas of these pregnancies with those of normal pregnancies. Their results showed the former to have a significantly larger amount of trophoblastic tissue. The amount of hCG secreted by each trophoblast is increased as well [17], partially due to a response to hypoxia [15]. This mechanism of compensation may be a consequence of any ischemic or hypoxic damage to the placenta or perhaps occurs as a result of damage to the placental/fetal vessels or an increase in their resistance. The hCG levels decrease throughout the second trimester. The delayed decrease in hCG levels in the pregnancies with elevated levels could be explained by the compensation of the placenta to its slow-growing fetus.

In our study there was only one case of trisomy 21. The hCG level in that pregnancy was 4.39 MOM. Combining the results of our study with those of an earlier study by Palacio and collaborators [18], there was only one case of aneuploidy in 80 pregnancies (1.25%) at hCG levels above 5 MOM and none at hCG levels above 6 MOM. At present the calculation of the risk for Down syndrome with hCG levels above 4 MOM is done without knowing the true occurrence of Down syndrome in this group, by extrapolating the known risk for Down syndrome for low levels of hCG. As a result, the importance of the hCG level might be exaggerated in calculating the probability equation for Down syndrome for high hCG levels. After collecting more data on this rare subgroup, it may be necessary to adjust the Down syndrome probability equation at high levels of hCG. These adjustments may require decreasing the impact of the hCG level on the equation result. To our knowledge, our work and that of Palacio et al. reflects the largest group studied with these levels of hCG. The result of the Down syndrome probability equation is crucial for deciding whether or not to perform amniocentesis. Therefore it is important to provide the mother with the most accurate calculation.

We conclude that the level of hCG seems to be proportionate to the frequency and severity of complications. Down syndrome appears to be more common in the medium elevated hCG levels (2–4 MOM), perhaps due to the fact that it reflects limited damage to the placenta/fetus and therefore does not induce the placenta to secrete extreme levels of hCG.

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