Archives of Gynecology and Obstetrics (2019) 299:713–718
https://doi.org/10.1007/s00404-019-05041-y

MATERNAL- FETAL MEDICINE

Association between serum beta-human chorionic gonadotropin and preeclampsia and its effects on perinatal and maternal outcomes: a case control study

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Received: 18 May 2018 / Accepted: 5 January 2019 / Published online: 31 January 2019

Abstract

Purpose The aim of this study was to evaluate the relationship between serum beta-human chorionic gonadotropin (β-hCG) and preeclampsia (PE) and the effects of βhCG on maternal and perinatal outcomes.

Methods This case–control study included 125 pregnant women who were admitted to the labor ward of the Maternity Teaching Hospital, Erbil City, Kurdistan, Iraq between January and December 2016. Participants included 50 women with severe PE, 25 with mild PE, and 50 who were normotensive. Serum β-hCG concentrations during labor were compared between groups and maternal and perinatal outcomes were recorded.

Results There were no significant differences in maternal age or parity distribution between the three groups. Gestational age was less than 37 weeks in 34% of the women with severe PE and in 12% of women in the mild PE and normotensive groups ($p = 0.012$). Mean β-hCG concentration was 37,520.56 mIU/mL in women with severe PE, 16,487 mIU/mL in those with mild PE, and 11,699.82 mIU/mL in those who were normotensive ($p < 0.001$). There were no significant differences in perinatal outcomes between groups; however, those with β-hCG concentrations ≥ 40,000 mIU/mL had worse neonatal outcomes (lower Apgar scores, higher rate of NICU admission, and lower survival rate) and unfavorable maternal outcomes (seizures, abruption, post-partum hemorrhage, and deep vein thrombosis).

Conclusions There was a significant difference in β-hCG concentrations between women with PE and normotensive women. There were no significant differences in perinatal or maternal outcomes between groups, except in patients with β-hCG ≥ 40,000 mIU/mL.

Keywords β-hCG · Maternal outcome · Preeclampsia · Perinatal outcome

Introduction

Preeclampsia (PE), a relatively common pregnancy-specific disorder, is dangerous for mother and infant and unpredictable in onset and progression; the only known treatment is delivery [1]. The causes of PE are poorly understood. Several theories about its causes have been proposed and various biochemical markers have been found to be associated with its development. Some studies have used human chorionic gonadotrophin (hCG) concentrations alone as a biomarker [2], whereas other have used hCG in combination with maternal serum alpha fetoprotein (AFP), pregnancy-associated plasma protein A (PAPP-A), and serum inhibin A [3, 4].

Ongoing research continues to identify factors that indicate this is a heterogeneous disease. hCG appears to be involved in many aspects of angiogenesis and immune tolerance, suggesting that its dysregulation leads to pregnancy complications such as preeclampsia. This dysregulation could manifest as altered concentrations of hCG [5].

Published studies have differed regarding the gestational age at which β-hCG is evaluated and correlations between β-hCG concentrations and PE severity in different trimesters of pregnancy. One study compared β-hCG concentrations in pregnant women with PE after admission to the eclampsia ward in the late second or third trimester with those

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of normotensive pregnant women attending an outpatient department and found that serum β-hCG concentrations were significantly higher in women with severe preeclampsia than in controls [6]. In other studies, these concentrations have been checked in the second trimester [7, 8] or at term [9, 10].

However, no published studies have evaluated β-hCG concentrations during labor in women with PE.

In this study, we measured β-hCG concentrations in pregnant women with and without PE before delivery in the labor ward of a public hospital and evaluated neonatal and maternal outcomes.

Materials and methods

Study design and setting

This case–control study included 125 pregnant women admitted to the labor ward of our Maternity Teaching Hospital, Erbil, Kurdistan region, Iraq: 50 with severe PE, 25 with mild PE, and 50 normotensive women. This is the only public tertiary care hospital in the Erbil Governorate. Most women have received no recorded antenatal care.

Duration of the study

This study was conducted between January and December, 2016.

Inclusion and exclusion criteria

The inclusion criteria in both groups were: age more than 18 years, singleton pregnancy, either in labor or having labor induced because of preeclampsia, delivered vaginally or by emergency cesarean section, delivery by elective cesarean section because of PE or other indications in control group, and agreement to participate in the study.

The exclusion criteria were: age less than 18 years, diabetes mellitus, chronic hypertension, renal disease, multiple gestations, moderate PE, smoker and refusal to participate.

Baseline maternal characteristics (age, body mass index, gestational age, and mode of delivery) were compared between the three groups. All information about the women was recorded in a questionnaire designed for the study that was completed in a face-to-face interview after written informed consent had been obtained.

Estimation of required sample size

The participants were collected by convenience sampling. The required sample size was determined using PS software (power and sample size collection version 3.0.12). The following information was entered into the program: $\alpha = 0.01$; power = 0.09; estimated proportion of high hCG concentrations 0.3 in women with PE and 0.02 in control women (6). The estimated sample size was 48 women with PE and 48 controls.

Study procedure

This study was undertaken in the labor ward after a maternal history had been obtained (age, parity, duration of PE, whether receiving treatment) and systolic and diastolic blood pressure measured in the right and left arms. Blood pressure was checked after about 20 min of rest while obtaining informed consent for participation. It was measured with a mercury sphygmomanometer and an appropriately sized cuff at the level of the heart, with the women reclining at a 45° angle [11]. Severe PE was defined as severe hypertension with or without symptoms and/or biochemical and/or hematological abnormalities. PE was defined as new hypertension with significant proteinuria after 20 week gestation. Severe hypertension was defined as a systolic blood pressure of 160 mmHg or greater or diastolic blood pressure of 110 mmHg or greater, whereas mild hypertension was defined as systolic blood pressure of 140–149 mmHg or diastolic blood pressure of 90–99 mmHg [11]. All diagnoses of PE, including in women with severe PE that had been diagnosed before delivery, with PE diagnosed for the first time during delivery, and with mild PE, were made in accordance with the Nice guideline [11]. The controls comprised normotensive women.

Visually read reagent strips (Dreadnought Trading Estate, Bridport, Dorset, UK) were used to assess proteinuria in patients who were admitted and first diagnosed with PE when delivery was imminent and could not be delayed. A result of + 1 was considered significant proteinuria. Women were asked to wash their perineum and collect mid-stream urine in a test tube for testing. In contrast, participants who were known to have severe or mild preeclampsia and were enrolled in the study on the date of delivery had 24 h urinary protein measured prior to admission for delivery.

In all the participants, blood pressure was checked frequently during labor and during preparation for Cesarean section. A diagnosis of PE was confirmed by recording of high-blood pressure on two occasions 4 h apart.

β-hCG was measured with a radioimmune assay (Roche-Cobas e 411; Roche Diagnostics GmbH D, Mannheim, Germany). Two mL of venous blood was obtained and immediately sent to the lab, where it was centrifuged to obtain serum. β-hCG concentrations are expressed as mIU of hCG per mL of blood. Gestational age was confirmed either by dates or ultrasound. The mode of delivery was classified as vaginal (spontaneous or induced), elective cesarean section (CS; for previous scar, infertility, PE,

fetal malposition), or emergency CS (for fetal indications, abruption, poor progress in second stage of labor, and eclampsia). No participants were delivered by operative vaginal delivery. After delivery, the newborn was weighed and Apgar scores obtained at 1 and 5 min. Apgar scores were classified as severely depressed (0–3), moderately depressed (4–6), or excellent (7–10) [12].

Admissions to the neonatal intensive care unit (NICU) were recorded and infants followed for the first week of life. The mothers were monitored after delivery for development of complications, including eclamptic seizures and primary post-partum hemorrhage (PPH). In the first week after delivery, mothers were reassessed for development of deep vein thrombosis (DVT), pulmonary embolism, and secondary PPH. Primary PPH was defined as loss of 500 mL or more of blood from the reproductive tract within 24 h after delivery, whereas secondary PPH was defined as abnormal vaginal bleeding during the first 12 weeks after delivery [13].

Statistical analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS, version 22). The χ^2 test for associations was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells in a table was less than 5. One-way analysis of variance (ANOVA) was used to compare three means. A post hoc test (least significant difference) was used to compare means between groups (after ANOVA). A p value of ≤ 0.05 was considered to denote statistical significance.

Results

One hundred and forty-three pregnant women were interviewed. Ten were excluded, because they had moderate preeclampsia, three were lost to follow-up, because they moved away, two did not respond to attempts at phone contact, and three refused to complete the interview. Thus, our study sample included 125 pregnant women.

The mean maternal age ± standard deviation was 27 ± 4.7 years (range 20–39 years; median, 27 years). The study sample included three groups of women: severe PE ($n=50$), mild PE ($n=25$), and normotensive ($n=50$).

As shown in Table 1, the commonest age range was 25–29 years (36%); 34.4% of participants were aged 20–24 years. There was no significant difference in age distribution between the three groups ($p=0.759$). Most women (77.6%) were multiparous; there were no significant differences in parity distribution between the three groups ($p=0.537$). As shown in Table 1, 34% of the women with severe PE had a gestational age of less than 37 weeks, compared with 12% of women in both the mild PE and normotensive groups; this difference was statistically significant.

As shown in Table 2, mean β-HCG concentrations differed significantly between the women with severe and mild PE and those who were normotensive.

Table 3 shows that the highest rate (10%) of PPH was in the severe PE group, compared with 4% each in the mild PE and normotensive groups; however, this difference is not statistically significant ($p=0.566$). One woman in the severe PE group developed a DVT ($p=1$). Five women (10%) in the severe PE group developed eclampsia, whereas no women in the mild PE or normotensive groups did ($p=0.024$).

Table 1 Distribution of samples by age, parity, and gestational age

	Severe PE	Mild PE	Normotensive	Total	*p*
Age (years)					
20–24	18 (36.0%)	9 (36.0%)	16 (32.0%)	43 (34.4%)	
25–29	15 (30.0%)	9 (36.0%)	21 (42.0%)	45 (36.0%)	
30–34	11 (22.0%)	6 (24.0%)	11 (22.0%)	28 (22.4%)	
≥35	6 (12.0%)	1 (4.0%)	2 (4.0%)	9 (7.2%)	0.759*
Parity					
Primiparous	12 (24.0%)	4 (16.0%)	7 (14.0%)	23 (18.4%)	
Multiparous	35 (70.0%)	20 (80.0%)	42 (84.0%)	97 (77.6%)	
Grand multiparous	3 (6.0%)	1 (4.0%)	1 (2.0%)	5 (4.0%)	0.537*
Gestational age (weeks)					
<37	17 (34.0%)	3 (12.0%)	6 (12.0%)	26 (20.8%)	
≥37	33 (66.0%)	22 (88.0%)	44 (88.0%)	99 (79.2%)	0.012
Total	50 (100.0%)	25 (100.0%)	50 (100.0%)	125 (100.0%)	

PE preeclampsia

*By Fisher's exact test

Table 2 βHCG concentrations according to study group

Group	*N*	Mean β HCG	SD	*p* (ANOVA)	LSD groups	*p* (LSD)
(A) Severe PE	50	37,520.56	5966.74		A vs. B	< 0.001
(B) Mild PE	25	16,487.28	1233.26	< 0.001	A vs. C	< 0.001
(C) Normotensive	50	11,699.82	1232.35		B vs. C	< 0.001
Total	125	22,985.61	12,650.01			

B-hCG beta-human chorionic gonadotropin, *LSD* least significant difference, *PE* preeclampsia

Table 3 Unfavorable maternal outcomes

	Severe PE *N* = 50		Mild PE *N* = 25		Normotensive *N* = 50		*p*
	No.	(%)	No.	(%)	No.	(%)	
PPH	5	(10.0)	1	(4.0)	2	(4.0)	0.566
DVT	1	(2.0)	0	(0.0)	0	(0.0)	1.000
Eclampsia	5	(10.0)	0	(0.0)	0	(0.0)	0.024

DVT deep venous thrombosis, *PE* preeclampsia, *PPH* post-partum hemorrhage

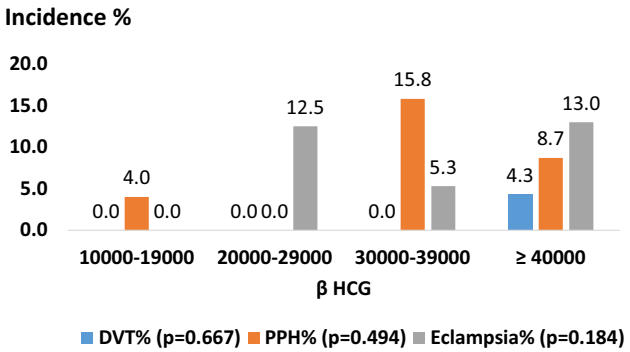

Fig. 1 Relationship between β-hcG titers and maternal outcomes

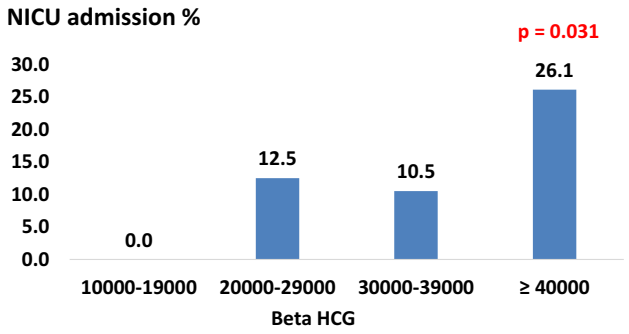

Fig. 2 Relationships between β-hCG titers and NICU admissions. *Beta hCG* beta human chorionic gonadotropin, *NICU* neonatal intensive care unit

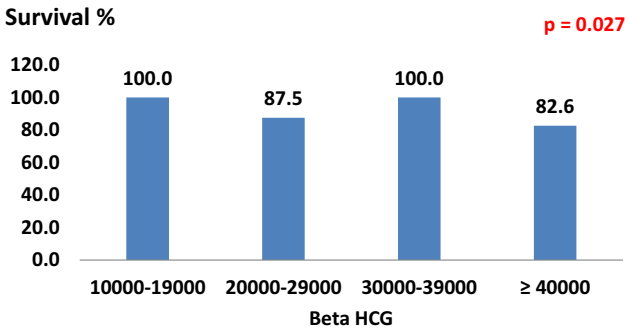

Fig. 3 Relationship between β-hCG titers and neonatal survival in the first week. *Beta hCG* beta human chorionic gonadotropin

There were no statistically significant differences in associations between maternal outcomes and hCG concentrations (Fig. 1).

The rate of admission to the neonatal intensive care unit (NICU) was 18% in the severe PE group and 10% in the normotensive group; none of the neonates in the mild PE group required admission to the NICU ($p = 0.062$). Only one neonate (in the severe PE group) had a birth weight of less than 2500 grams. There were no significant differences in survival rates between the three study groups ($p = 0.212$). All neonates in the mild PE group and 88% in the normotensive group had normal Apgar scores at 1 min, compared with 74% of neonates in the severe PE group ($p = 0.011$). At 5 min, the Apgar scores in the severe PE group had improved and the differences between the groups were no longer significant ($p = 0.362$).

There was a significant relationship between hCG concentrations, neonatal survival, and admission to neonatal care units (Figs. 2, 3). Newborns in the subgroup of women with PE and hCG > 40,000 mIU/mL were more often admitted to the NICU (six newborns of 23 women) and more often died (four newborns of 23 women) (Table 4).

Table 4 Neonatal outcomes

	Severe PE		Mild PE		Normotensive		*p*
	No.	%	No.	%	No.	%	
NICU							
Yes	9	18.0	0	0.0	5	10.0	0.062
No	41	82.0	25	100.0	45	90.0	
Survival							
Yes	45	90.0	25	100.0	48	96.0	0.212*
No	5	10.0	0	0.0	2	4.0	
APGAR score in the first minute							
0–3	1	2.0	0	0.0	2	4.0	0.011*
4–6	12	24.0	0	0.0	4	8.0	
7–10	37	74.0	25	100.0	44	88.0	
APGAR score in the fifth minute							
4–6	4	8.0	0	0.0	4	8.0	0.362*
7–10	46	92.0	25	100.0	46	92.0	
Weight (g)							
< 2500	1	2.0	0	0.0	0	0.0	1*
≥ 2500	49	98.0	25	100.0	50	100.0	
Total	50	(100.0)	25	(100.0)	50	(100.0)	

NICU neonatal intensive care unit

*By Fisher's exact test

Discussion

The high-blood pressure in women with PE results from vasoconstriction and impaired angiogenesis, which leads to hypoxia and hyperplasia of trophoblastic cells, which in turn causes hypersecretion of placental hormone, ultimately leading to high concentrations of circulating β-hCG [3]. In the current study, we found significantly higher β-hCG concentrations in women with severe PE than in those with mild PE or normotension.

A study performed at Dhaka Medical College Hospital in 2014 involving 74 pregnant women with PE and 76 normotensive women found that β-hCG concentrations were highest in women with severe PE and lowest in normotensive pregnant women, whereas women with mild PE had intermediate concentrations ($p < 0.001$) [6].

A study conducted in Istanbul, Turkey in 2004 compared β-hCG concentrations in 80 women with mild PE, severe PE, superimposed hypertension, or chronic hypertension with those in 25 normotensive pregnant women. Mean reported β-hCG concentrations were 17,000 mIU/mL in women with mild PE, 49,000 mIU/mL in women with severe PE, 41,000 mIU/mL in women with superimposed hypertension, 12,558 mIU/mL in women with chronic hypertension, and 9647 mIU/mL in normotensive women. β-hCG concentrations were significantly higher in women with severe PE than in the other groups ($p < 0.001$) [14]. In another study published in the *International Journal of Biomedical and Healthcare Science* in 2016 that included 500 pregnant women at 16–24 weeks of gestation in which urea, uric acid, and β-hCG concentrations were evaluated, it was found that all three variables were significantly higher in women with mild or severe PE than in normotensive women ($p < 0.001$) [15].

In this study, we used β-hCG as a biochemical marker for predicting maternal and fetal outcomes in women with severe PE. A study published in the *Journal of Obstetrics and Gynecology* in 2012 used serum hCG in early pregnancy as a marker for the development of pregnancy-induced hypertension. The authors of that study concluded that hCG concentrations may reflect the degree of disordered activity of placental trophoblasts in pregnancy-induced hypertension and can be used as a marker for this disorder [16]. We found a higher rate of NICU admission and early neonatal death among women with severe PE. Unfavorable neonatal outcomes were more common in women with β-hCG concentrations above 40,000 mIU/mL. As to maternal outcomes, there were higher rates of abruption, PPH, DVT, and eclamptic seizures in women with severe PE; however, there were no statistically significant differences in relationship to hCG concentrations.

One strength of this study was that it investigated high hCG concentrations as a marker for sever PE and adverse maternal and perinatal outcomes, which has rarely been previously reported.

A limitation of the study is that we did not include women with moderate PE; future studies were advised to include this group. Another limitation is that in women admitted in labor and with no recorded prenatal care, the diagnosis of

mild and severe PE depended on strip tests for proteinuria. In addition, the sample size was too small to compare fetal and maternal outcomes between groups.

Acknowledgements The research team would like to thank all the women who generously shared their time and agreed to participate in this study. Special thanks to Professor Namir G. Al.Hawler Medical University, College of Medicine, Department of Community Erbil, Kurdistan Region, Iraq for helping with data analysis. We also thank Rebecca Tollefson, DVM, and Trish Reynolds, MBBS, FRACP, from Edanz Group (www.edanzediting.com/ac) for editing drafts of this manuscript.

Author contributions SIT data collection, manuscript writing, and data analysis. SKA project development, manuscript revision, and data management.

Funding This work was supported by the Kurdistan Board for Medical Specialties. Financial support was for academic purposes only.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study was conducted in accordance with the ethical standards of the Ethics and Scientific Committee of Kurdistan Board of Medical Specialties Nb. 30/0217 and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent to participate in the study was obtained from each woman. Participants were assured that confidentiality would be maintained and that their information would be used for research purposes only.

References

1. Redman CWG (1991) Current topic: pre-eclampsia and the placenta. Placenta 12:301–308
2. Hsu CD, Chan DW, Iriye B, Johnson TRB, Hong SF, Repke JT (1994) Elevated serum human chorionic gonadotropin as evidence of secretory response in severe preeclampsia. Am J Obstet Gynecol 170:1135–1138
3. Salas SP, Marshall G, Gutierrez BL, Rosso P (2005) Time course of maternal plasma volume and hormonal changes in women with preeclampsia or fetal growth restriction. Hypertension 47:203–208
4. Soundararajan P, Muthuramu P, Veerapandi M, Mariyappan R (2016) Serum beta chorionic gonadotropin and lipid profile in early second trimester (14–20 weeks) is a predictor of pregnancy-induced hypertension. Int J Reprod Contracept Obstet Gynecol 5:3011–3016
5. Norris W, Nevers T, Sharma S, Kalkunte S (2011) Review: hCG, preeclampsia and regulatory T cells. Placenta 32(Suppl 2):S182–S185. https://doi.org/10.1016/j.placenta.2011.01.009
6. Begum Z, Ara I, Tanira S, Keya KA (2014) The association between serum beta-human chorionic gonadotropin and preeclampsia. J Dhaka Med Coll 23:89–93
7. Hsu CD, Chan DW, Iriye B, Johnson TRB (1994) Elevated serum human chorionic gonadotropin as evidence of secretory response in severe preeclampsia. Am J Obstet Gynecol 170(4):1135–1138
8. Önderoğlu LS, Kabukçu A (1997) Elevated second trimester human gonadotropin level associated with adverse pregnancy outcome. Int J Gynaecol Obstet 6(3):245–249
9. Choudhury K, Das M, Ghosh S, Bhattacharya D, Ghosh TK (2012) Value of serum β-HCG in pathogenesis of pre-eclampsia. J Clin Gynecol Obstet 1(4–5):71–75
10. Gökdeniz R, Ariguloğlu E, Bazoğlu N, Balat Ö (2000) Elevated serum β-hCG levels in severe preeclampsia. Turk J Med Sci 30:43–45
11. National Institute for Health and Care Excellence (2010) Hypertension in pregnancy: diagnosis and management. NICE clinical guideline CG107. https://www.nice.org.uk/guidance/CG107. Accessed 11 Oct 2018
12. Committee on Obstetric practice American Academy of Pediatrics -Committee on Fetus and Newborn (2015) No. 644: The Apgar score. Obstet Gynecol 126(4):252–255. https://doi.org/10.1097/AOG0000000000001108
13. Royal College of Obstetricians and Gynecologists (2016) Postpartum hemorrhage, prevention and management (Green-top Guideline No. 52). https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.14178. Accessed 11 Oct 2018
14. Gubuz A, Karateke A, Mengulluoglu M, Gedikbasi A, Ozturkmen M, Kabaca C et al (2004) Can serum hCG values be used in the differential diagnosis of pregnancy complicated by hypertension? Hypertens Pregnancy 23:1–12
15. Yadav V, Verma AK, Soni N, Kaushik GG (2016) Broca JS (2016) Serum level of beta human chorionic gonadotropin in pathogenesis of pre-eclampsia. IJBHS 6(2):219–256
16. Kaur G, Jain V, Mehta S, Himani S (2012) Prediction of PIH by maternal serum beta HCG levels in the second trimester (13–20 weeks) of pregnancy. J Obstet Gynaecol India 62:32–34