

Maternal Cytoglobin Levels In Preeclampsia Versus Normal Pregnancy in the Late Third Trimester

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Abstract:

Objective: The objectives were to compare maternal cytoglobin levels in preeclamptic women versus normal pregnant women, and to compare maternal and neonatal outcomes between preeclampsia and normal pregnancy.

Material and Methods: The cross-sectional analytical study was conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University. Forty-two preeclamptic pregnant women and 42 normal pregnant women were included. Blood was collected in nonheparinized tubes, centrifuged, and stored at -80°C until assayed. Maternal serum cytoglobin levels were measured by enzyme-linked immunosorbent assays.

Results: Mean serum cytoglobin levels in preeclamptic women were not different from those of normal pregnancy (4.7 ± 1.3 vs 5.1 ± 1.3 ng/mL, p -value=0.204). However, serum cytoglobin levels were higher in early-onset preeclamptic women ($n=5$) than in normal pregnancy ($n=5$) at the same gestational age (5.6 ± 0.8 vs 3.8 ± 0.9 ng/mL, p -value=0.023). Preeclamptic women had a higher cesarean section rate than normal pregnant women (69.0 % vs 33.3 %, p -value=0.004) and had a lower neonatal birth weight than normal pregnant women ($2,744.0 \pm 777.8$ vs $3,135 \pm 576.2$ grams, p -value=0.01). Admission to the neonatal intensive care unit was higher in preeclamptic women than in normal pregnant women (21.4% vs 2.4%, p -value=0.015).

Conclusion: No significant difference in cytoglobin levels was observed between women with preeclampsia and normal controls. However, a significant difference in cytoglobin levels was observed between a small number of early-onset preeclampsia cases and gestational age-matched normal controls, a finding that requires confirmation in larger future studies.

Keywords: cytoglobin, ELISA, preeclampsia, pregnancy outcome

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Introduction

Preeclampsia is a serious obstetric complication that causes maternal and perinatal morbidity and mortality, affecting 5–10% of all pregnancies. The World Health Organization (WHO) stated that hypertensive disorders were the cause of 16% and 9–26% of maternal deaths in high-income and low-income countries, respectively¹. This complication is costly, and there are screening tests for preeclamptic pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE) guidelines recommend screening pregnant women based on clinical risk factors; however, this approach achieves detection rates of 41% and 34%, with a 10% false-positive rate, for preterm and term preeclampsia, respectively^{2,3}. A combination of maternal factors and measurements of mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor yields a higher detection rate⁴. Many theories suggest the etiology of preeclampsia. The exact etiology is still unknown. An inadequate trophoblastic invasion is widely accepted as one etiology. It leads to insufficient spiral artery remodeling and impaired placental blood flow, which then causes a hypoxic placental environment^{5–7}. Placental hypoxia, as a key pathogenic mechanism of preeclampsia, is more commonly associated with early-onset disease⁸.

Cytoglobin is classified as a non-erythroid globin, along with human proteins, such as myoglobin, neuroglobin, androglobin, and hemoglobin α , because it is found outside the red blood cells⁹. It has recently been described as a stress-responsive hemoprotein that is phylogenetically preserved in humans, rats, and mice^{10,11}. Cytoglobin can bind to oxygen, nitric oxide, and free radicals during oxidative stress induced by ischemic/hypoxic conditions. This supports the potential cytoprotective role of cytoglobin^{12,13}. Cytoglobin was regulated by hypoxia through the transactivation of hypoxia-inducible factor-1 α ¹⁴. Given the important role of placental hypoxia in the pathogenesis

of preeclampsia^{15,16}, cytoglobin levels should be higher in preeclamptic pregnancy. Only one study found that cytoglobin levels were higher in preeclampsia¹¹. Thus, the primary objective was to compare maternal cytoglobin levels in pregnant women with preeclampsia and normal pregnant women. The secondary objective was to compare maternal and neonatal outcomes between pregnant women with preeclampsia and normal pregnant women.

Material and Methods

This was a cross-sectional analytical study carried out at the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, from March 2020 to March 2021. The Institutional Review Board of the Faculty of Medicine of Chulalongkorn University approved the research protocol (IRB no. 112/63). The study has adhered to the Declaration of Helsinki guidelines. Pregnant women aged 18 to 45 years and gestational age (GA) more than 20 weeks who were diagnosed with preeclampsia were enrolled in the study. Exclusion criteria were multiple pregnancies, premature rupture of membranes, pregnant women with fetal abnormalities, overt or gestational diabetes, systemic diseases, such as chronic hypertension, and autoimmune diseases. The control cases were healthy pregnant women with the same gestational age admitted with the next admission number after the preeclamptic women. The sampling method was convenience sampling. Pregnant women who met the inclusion criteria were invited. All participants received the study information and signed an informed consent form prior to participating in this study.

Preeclampsia was defined as new-onset hypertension (blood pressure [BP] of at least 140/90 mmHg) in pregnancies over 20 weeks of gestation, accompanied by proteinuria (more than 300 mg/24 hours, more than 2+ in urine dipstick, or urine protein-creatinine ratio >0.3)¹⁷. Severe preeclampsia was defined as having a BP at

least 160/110 mmHg at least 4 hours apart and/or new-onset cerebral or visual disturbances, pulmonary edema, thrombocytopenia, persistent severe right upper quadrant, epigastric pain, impaired liver function, or progressive renal insufficiency¹⁷. Late-onset preeclampsia was defined as preeclampsia that occurred in GA 34 weeks or more¹⁸, while early-onset preeclampsia was defined as preeclampsia that occurred at GA <34 weeks¹⁸. Composite maternal outcomes included postpartum hemorrhage, postpartum endometritis, and surgical wound infection. Composite neonatal complications included small for gestational age, neonatal intensive care unit admission, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, and neonatal death.

The mean and standard deviation of cytoglobin in preeclamptic pregnancy and the control from the previous study were used for the calculation of the sample size¹¹. Therefore, 42 cases with preeclampsia and 42 controls were required for the study ($\alpha=0.05$, $\beta=0.2$).

Five milliliters of venous blood from participants were collected in non-heparinized tubes and centrifuged. Serum was stored at -80°C until assayed. Cytoglobin levels were determined using enzyme-linked immunosorbent assay (ELISA) techniques (human cytoglobin ELISA kit, RayBiotech Life, Inc., USA). The intra-assay and inter-assay variations were <10%. Maternal and neonatal outcomes were recorded.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM, New York, USA). Data were described as percentages, means with standard deviations (S.D.), and medians with interquartile ranges (IQR). Categorical variables were analyzed using the chi-square test and Fisher's exact test. Continuous variables were analyzed using the Independent *t*-test. Nonparametric continuous variables were analyzed using the Mann-Whitney U test. A $p\text{-value}<0.05$ was considered statistically significant.

Results

A total of 84 pregnant women were enrolled in the study (42 women with preeclampsia and 42 control pregnant women). Late-onset preeclampsia occurred in 37 cases, while early-onset preeclampsia occurred in 5 cases. Severe preeclampsia occurred in 14 cases, while mild preeclampsia occurred in 28 cases. Demographic data are shown in Table 1. There were no significant differences between the two groups in age at blood sampling, maternal body mass index, parity, family history of preeclampsia, history of preeclampsia, and total weight gain. Gestational age at the time of blood sampling was significantly different between the two groups. Serum cytoglobin levels were not different between preeclamptic women and normal pregnancy (5.1 ± 1.3 vs 4.7 ± 1.3 ng/mL, $p\text{-value}=0.204$) (Table 2).

A subgroup analysis comparing early-onset preeclampsia ($n=5$) with gestational age-matched normal pregnancies ($n=5$) was performed. The control cases were healthy pregnant women with the same gestational age admitted with the next admission number after preeclamptic women. The baseline demographic characteristics were not different. Serum cytoglobin levels were higher in early-onset preeclamptic women than normal pregnancy (5.6 ± 0.8 vs 3.8 ± 0.9 ng/mL, $p\text{-value}=0.023$) (Table 3). The rationale for matching normal pregnancies by gestational age in the early-onset preeclampsia subgroup analysis was to minimize confounding factors associated with gestational age.

The maternal and neonatal outcomes are shown in Table 2. Women with preeclampsia had a higher rate of cesarean section than normal pregnancy (69.0 % vs 33.3 %, $p\text{-value}=0.004$). Regarding neonatal outcomes, women with preeclampsia had a lower neonatal birth weight than normal pregnancy ($2,744.0\pm777.8$ vs $3,135 \pm 576.2$ grams, $p\text{-value}=0.01$). Composite neonatal complications were significantly higher in preeclampsia. There was a higher

Table 1 Baseline characteristics and serum cytoglobin levels

Baseline characteristics	Preeclampsia (n=42)	Control (n=42)	p-value
Age	32.7±5.4	30.7±5.8	0.102
Gestational age at blood sampling (weeks)	37 (36, 39)	39 (38, 39)	0.001
Multiparity	13 (30.9%)	13 (30.9%)	>0.99
Elderly gravidarum (age ≥35 years)	13 (31.0%)	11 (26.2%)	0.629
Teenage pregnancy	0	1 (2.4%)	>0.99
Body mass index (kg/m ²)	22.5 (20.4, 24.9)	21 (18.7, 24.6)	0.039
Obesity (BMI ≥30 kg/m ²)	2 (4.8%)	1 (2.4%)	>0.99
Family history of preeclampsia	0	0	>0.99
History of preeclampsia	0	0	>0.99
Total weight gain (kgs)	15.3±6.6	15.1±5.1	0.901
Excessive weight gain (>20 kgs)	7 (16.7%)	5 (11.9%)	0.533

Data are shown as mean±standard deviation, median (interquartile range), or n (%), BMI=body mass index

Table 2 Serum cytoglobin and maternal and neonatal outcomes

	Preeclampsia (n=42)	Control (n=42)	p-value
Serum cytoglobin (ng/mL)	5.1±1.3	4.7±1.3	0.204
Maternal outcome			
Gestational age at delivery (weeks)	37 (36, 39)	39 (38, 40)	<0.001
Preterm delivery	7 (16.7%)	2 (4.8%)	0.156
Route of delivery			0.004
Low transverse cesarean section	29 (69%)	14 (33.3%)	
Vaginal route	13 (31%)	28 (66.7%)	
Composites maternal complications	3 (7.1%)	3 (7.1%)	>0.99
Length of stay (days)	5.1±2.3	4.5±1.7	0.137
Neonatal outcome			
Birth weight (grams)	2,744.0±777.8	3,135.2±576.2	0.01
Sex			0.507
Male	26 (61.9%)	23 (54.8%)	
Female	16 (38.1%)	19 (25.2%)	
Apgar at 1 min <7	6 (14.3%)	1 (2.4%)	0.099
Apgar at 5 min <7	1 (2.4%)	0	>0.99
Composite neonatal complications	15 (35.7%)	2 (4.8%)	0.001
Neonatal intensive care unit admission	9 (21.4%)	1 (2.4%)	0.015
Respiratory distress syndrome	4 (9.5%)	1 (2.4%)	0.36
Neonatal sepsis	5 (11.9%)	2 (4.8%)	0.433
Small for gestational age	10 (23.8%)	1 (2.4%)	0.007
Neonatal death	0	1 (2.4%)	>0.99
Length of stay (days)	10.2±15.5	5.9±9.2	0.122

Data are shown as mean±standard deviation, median (interquartile range), or n (%)

Table 3 Serum cytoglobin and maternal and neonatal outcomes between early-onset preeclampsia and controls

	Early-onset preeclampsia (n=5)	Control (n=5)	p-value
Serum cytoglobin (ng/mL)	5.6±0.8	3.8±0.9	0.023
Maternal outcome			
Gestational age at delivery (weeks)	31 (29.5, 33)	37 (30.5, 41)	0.151
Preterm delivery	1 (20%)	0	>0.99
Route of delivery			0.048
Low transverse cesarean section	5 (100%)	1 (20%)	
Vaginal route	0	4 (80%)	
Composites maternal complications	1 (20%)	1 (20%)	>0.99
Length of stay (days)	4.6±1.5	3.6±1.7	0.351
Neonatal outcome			
Birth weight (grams)	1,290±419.5	2,683.2±1,117.1	0.016
Sex			>0.99
Male	2 (40%)	2 (40%)	
Female	3 (60%)	3 (60%)	
Apgar at 1 min <7	3 (60%)	1 (20%)	0.523
Apgar at 5 min <7	0	0	NA
Composite neonatal complications	5 (100%)	2 (40%)	0.167
Neonatal intensive care unit admission	5 (100%)	1 (20%)	0.048
Respiratory distress syndrome	2 (40%)	1 (20%)	>0.99
Neonatal sepsis	3 (60%)	1 (20%)	0.524
Small for gestational age	3 (60%)	1 (20%)	0.524
Neonatal death	0	1 (20%)	>0.99
Length of stay (days)	39.8±28.3	16±26.3	0.206

Data are shown as mean±standard deviation, median (interquartile range), or n (%)

rate of neonatal complications (small for gestational age and admission to the neonatal intensive care unit) in the preeclampsia group. Serum cytoglobin levels and maternal and neonatal outcomes across the three groups—early-onset preeclampsia, late-onset preeclampsia, and normal controls—are shown in Table 4.

Discussion

This study revealed that maternal serum cytoglobin levels in overall preeclampsia were not different than those in normal pregnant women; however, serum cytoglobin levels were higher in women with early-onset preeclampsia than in normal pregnancy at the same gestational age.

The result of this study was different from a previous study that found serum cytoglobin levels were higher in the preeclamptic group¹¹. This finding applied to both early-onset and late-onset preeclampsia, but Tayyar et al. compared three groups: early-onset preeclampsia, late-onset preeclampsia, and normal controls⁽¹¹⁾. This difference between the studies may be due to the difference in race. The other explanation was that cytoglobin might not be involved in the main etiology of preeclampsia. Serum cytoglobin levels were higher in pregnant women with early-onset preeclampsia than in normal pregnancy in the same GA. This result was similar to the previous study¹¹. Early-onset preeclampsia has greater severity than late-

Table 4 Serum cytoglobin and maternal and neonatal outcomes comparing three groups: early-onset preeclampsia, late-onset preeclampsia, and normal controls

	Early-onset preeclampsia (n=5)	Late-onset preeclampsia (n=37)	Control (n=42)	p-value
Serum cytoglobin (ng/mL)	5.6±0.8	5.0±1.3	4.7±1.3	0.272
Maternal outcome				
Gestational age at delivery (weeks)	31 (29.5, 33)	38 (36.5, 39)	39 (38, 40)	<0.001
Preterm delivery	1 (20%)	6 (16.2%)	2 (4.8%)	0.177
Route of delivery				<0.001
Low transverse cesarean section	5 (100%)	24 (64.9%)	14 (33.3%)	
Vaginal route	0	13 (35.1%)	28 (66.7%)	
Composites maternal complications	1 (20%)	2 (5.4%)	3 (7.1%)	0.457
Length of stay (days)	4.6±1.5	5.1±2.4	4.5±1.7	0.277
Neonatal outcome				
Birth weight (grams)	1,290±419.5	2,940.4±579.7	3,135.2±576.2	<0.001
Sex				0.457
Male	2 (40%)	24 (64.9%)	23 (54.8%)	
Female	3 (60%)	13 (35.1%)	19 (25.2%)	
Apgar at 1 min <7	3 (60%)	3 (8.1%)	1 (2.4%)	0.001
Apgar at 5 min <7	0	1 (2.7%)	0	0.5
Composite neonatal complications	5 (100%)	10 (27%)	2 (4.8%)	<0.001
Neonatal intensive care unit admission	5 (100%)	4 (10.8%)	1 (2.4%)	<0.001
Respiratory distress syndrome	2 (40%)	2 (5.4%)	1 (2.4%)	0.016
Neonatal sepsis	3 (60%)	2 (5.4%)	2 (4.8%)	0.004
Small for gestational age	3 (60%)	7 (18.9%)	1 (2.4%)	0.001
Neonatal death	0	0	1 (2.4%)	>0.99
Length of stay (days)	39.8±28.3	6.2±6.7	5.9±9.2	<0.001

Data are shown as mean±standard deviation, median (interquartile range), or n (%)

onset preeclampsia. Early-onset preeclampsia may have a different pathophysiology from late-onset preeclampsia. Therefore, cytoglobin levels were higher in early-onset preeclampsia alone. This biomarker may be used to predict early-onset preeclampsia.

Inadequate trophoblastic invasion is the most accepted etiology of preeclampsia. It leads to insufficient spiral artery remodeling and impaired placental blood flow, which then causes the placenta to become a hypoxic environment⁶. Cytoglobin was regulated by hypoxia through transactivation of hypoxia-inducible factor-1α¹⁴. Thus, cytoglobin levels should be higher in preeclamptic pregnancy. However, cytoglobin in overall preeclampsia

was not different from normal pregnancy in this study. This may be because cytoglobin is not the main etiology of preeclampsia in this population.

There was a statistically significant difference in gestational age at the time of blood sampling between the groups. However, gestational age at the time of blood sampling did not affect cytoglobin levels. A previous study found that serum cytoglobin levels were not correlated with gestational age at the time of blood sampling¹¹.

The strengths of the present study were that it had more cases of preeclampsia than the previous study and that the cases and controls were collected during the same period. The limitation was that it was a cross-

sectional design, and there was a small number of women with early-onset preeclampsia. The clinical implications of using serum cytoglobin for early-onset preeclampsia remain preliminary. Therefore, the use of serum cytoglobin to predict early-onset preeclampsia needs further investigation. More studies with larger samples of women with early-onset preeclampsia should be performed to evaluate the role of cytoglobin.

Conclusion

No significant difference in cytoglobin levels was observed between women with preeclampsia and normal controls. However, a significant difference in cytoglobin levels was observed between a small number of early-onset preeclampsia cases and gestational age-matched normal controls, a finding that requires confirmation in larger future studies.

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Conflict of interest

No conflict of interest declared.

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