Second Trimester Serum Calprotectin in Prediction of Early Onset Preeclampsia

Original Article

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ABSTRACT

Objectives: To evaluate the association of serum calprotectin in early second trimester between 14th to 16th weeks and development of early onset preeclampsia <34wks.

Study design: This prospective observational study was conducted on 60 pregnant females at gestational age 14th to 16th weeks attending obstetrics clinic of ELShatby University Hospital, after approval of the local ethical committee and having informed written consent for every female included in the study.

Results: A total of 60 pregnant women participated in the study after applying inclusion and exclusion criteria. The overall incidence of preeclampsia in the study was 10%, while the incidence of Gestational hypertension was 15%. As regard serum calprotectin , there was no statistically significant difference between preeclamptic and non preeclamptic groups (p= 0.962).

Conclusion: The low levels of serum Calprotectin in the current study is most probably due to proteolysis either in vivo due to the uncontrolled MPO derived oxidative stress or pre-analysis, during sample handling and storage. Calprotectin proteolysis in the current work stands as a limitation in the use of CLP as a predictor of preeclampsia.

Key Words: Elshatby university hospital; preeclampsia; serum calprotectin.

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INTRODUCTION

Pregnancy-related hypertensive disorders are still a major global health concern for both mothers and their unborn children[1,2].

About 10% of pregnant women have hypertension, and about 25% of antenatal hospitalisations are due to pregnancy-related hypertension (gestational hypertension and pre-eclampsia)[1,2].

The following categories are used to classify hypertensive disorders of pregnancy according to the National High Blood Pressure Education Programme (NHBPEP) of the National Heart, Lung, and Blood Institute (NHLBI) and the modified classification by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[3,4]:

1. Gestational hypertension.
2. Chronic hypertension.
3. Preeclampsia.
4. Preeclampsia superimposed on pre-existing hypertension.

Gestational hypertension[2]:

Gestational hypertension refers to hypertension without proteinuria or other signs/symptoms of preeclampsia-related end-organ dysfunction that develops after 20 weeks of gestation. Ten to 25 percent of these patients may ultimately develop signs and symptoms of preeclampsia. Development of proteinuria upgrades the diagnosis to preeclampsia. Even without proteinuria, patients who develop severe hypertension or other features of severe disease are managed in the same way as those with preeclampsia with severe feature[2,5].

Chronic hypertension[2]:

Chronic hypertension is defined as hypertension that precedes pregnancy or is present on at least two occasions before the 20 week of gestation or persists longer than 12 weeks postpartum.

According to the etiology, it might be primary or secondary:

Essential hypertension is the most common reason of chronic hypertension, usually associated with family history of hypertension in addition to obesity.

Secondary causes of hypertension include primary renal disorders or primary hyperaldosteronism.

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Preeclampsia[2,5]:

Preeclampsia refers to the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation or postpartum in a previously normotensive patient[5].

Preeclampsia can be described as a pregnancy-specific syndrome which cause widespread vasospasm and vascular endothelial dysfunction[2,5].

According to the American College of Obstetrics and Gynaecology (ACOG) and the NHBPEP working group on high blood pressure in pregnancy:

Preeclampsia is defined: systolic blood pressure (SBP) greater than or equal to 140 mm Hg, diastolic blood pressure (DBP) more than or equal to 90 mm Hg, on two occasions as a minimum four hours apart in a patient who was previously normotensive patient and the co-occurrence of one or both of the resulting new-onset conditions[3]:

- Urine protein:creatinine ratio ≥30 mg/mmol[6].
- Additional signs of maternal organ dysfunction, such as involvement of the kidneys or the liver, neurological or hemorrhagic issues, or uteroplacental dysfunction[2,7].

Also mean arterial blood pressure (MAP) levels can be used to predict the future development of preeclampsia[8]. A second-trimester mean arterial blood pressure greater than or equal to 90 mm Hg is associated with preeclampsia[8]. For severe pre-eclampsia treatment protocols, a MAP threshold of 125 mm Hg has commonly been used as a cut-off point[9].

Preeclampsia superimposed upon existing hypertension[2,7]:

Preeclampsia is considered superimposed when it occurs in a patient with preexisting chronic hypertension. It is characterized by worsening or resistant hypertension (especially acutely), the new onset of proteinuria or a sudden increase in proteinuria, and/or significant new end-organ dysfunction after 20 weeks of gestation or postpartum in a patient with chronic hypertension.

Calprotectin:

Calprotectin is a heterodimer of the two calcium binding proteins S100A8 and S100A9. Calprotectin is present in the cytosol of various immune cell populations such as neutrophil granulocytes, monocytes, and macrophages and is expressed on the cell surface of monocytes and immature macrophages[10].

In neutrophils, for example, calprotectin is the main cytosolic component accounting for around 60% of the total soluble protein content. Upon activation of neutrophil granulocytes or after endothelial adhesion of monocytes, calprotectin is released into the interstitial tissue and the blood circulation as a proinflammatory response to infectious agents, tissue damage, and other cellular deviations such as cancer. It thereby serves as a danger-associated molecular pattern protein (DAMP) in the innate immune system[11].

Calprotectin has bacteriostatic and cytokine-like properties. Specifically, it enhances interleukin (IL)-1β secretion of interferon (IFN)-γ primed monocytes[12] and is associated with elevated levels of the pro-inflammatory serum cytokines IFN-γ, c-reactive protein, IL-6, tumor necrosis factor-β, and IL-17A[11].

In addition, calprotectin has been described to exert antimicrobial activity by depriving microorganisms of zinc[13].

Mononuclear phagocytes infiltrating a site of inflammation typically contain and express calprotectin, underlining its prominent role in the cellular immune response. Calprotectin has been associated with acute immunological activity, chronic inflammation, and other disorders, among them various human cancers[14].

Calprotectin can be measured in serum, plasma, and other body fluids such as meconium and amniotic fluid. In addition, high concentrations of calprotectin are found in stool. Fecal calprotectin has therefore been investigated as a marker of inflammatory activity in gastrointestinal disorders such as Crohn's disease, cystic fibrosis, ulcerative colitis, inflammatory bowel disease (IBD), and juvenile idiopathic arthritis[15,16]. For example, in a meta-analysis of 49 studies in >3000 IBD patients, fecal calprotectin demonstrated a pooled sensitivity of 85% and a specificity of 75% for diagnosing active IBD[17].

Beyond its diagnostic use in gastroenterology, it is also discussed as an inflammatory biomarker in rheumatology and nephrology. In rheumatoid arthritis, for example, both serum and synovial fluid calprotectin levels correlate with disease activity and radiographic disease progression[18]. In nephrology, calprotectin is a sensitive indicator of acute kidney injury in adult, pediatric, and transplant populations[19-21].

In contrast to IBD, rheumatology, and nephrology, the role of calprotectin in pregnancy and pregnancy-associated disorders is less well understood. Liosi *et al*., for example, assessed calprotectin in umbilical cord blood samples of term neonates and found that cord blood calprotectin concentrations at term were independent of intrauterine growth, gender, parity, and maternal age[22]. They concluded that calprotectin cord blood levels did not reflect the increased neutrophil activation and excessive apoptosis known to be associated with intrauterine growth restriction. On the other hand, plasma levels as well as

placental expression of calprotectin have been observed to be elevated among pregnant women with hypertensive disorders[23-24]. Since maternal, but not umbilical cord levels of calprotectin were found to be elevated, it has been hypothesized that calprotectin may be a potential marker of the maternal immune response to the pro-inflammatory endothelial activation in hypertensive disorders of pregnancy, but does not indicate changes in the fetal compartment[24].

Investigators have revealed leukocytes to be activated in pregnancy and to a higher degree in preeclamptic women compared to normotensive pregnant women.

Calprotectin is released from activated circulating leukocytes , thus the elevated maternal plasma calprotectin level found in preeclampsia supports the role of leukocyte activation in preeclampsia. Additional evidence is also found in the altered leukocyte adhesion molecule profile and intracellular reactive oxygen species demonstrated in the preeclamptic group of the same patient material as presented here (Holtheetal)[25].

The binding of zinc to calprotectin can inhibit enzymes such as matrix metalloproteinases (MMPs)[26].

The MMPs are of great importance in trophoblast invasion into the decidua during placentation at an early stage of pregnancy.

Preeclampsia is associated with reduced trophoblast invasion and reduced MMP-9 trophoblast expression at both the protein and the mRNA levels when compared to normal pregnancies, as well as low MMP-1 in decidual microvascular endothelial cells[26]. Whether an elevation of calprotectin is present during the placentation period in women with subsequent development of preeclampsia, and whether an augmented calprotectin level could affect placentation in vivo, remains to be seen.

AIM OF THE WORK

The aim of the study was to evaluate the association of serum calprotectin in early second trimester between 14th to 16th weeks and development of early onset preeclampsia <34wks.

PATIENTS AND METHODS

This prospective observational study was conducted on 60 pregnant females at gestational age 14th to 16th weeks attending obstetrics clinic of ELShatby university hospital, after approval of the local Ethical committee and having informed written consent for every female included in the study.

All patients were subjected to the following:

1. Complete history taking (gynecological, obstetric, medical, surgical).
2. Thorough examination with careful measurement of blood pressure starting from 16-14 wks.
3. Laboratory investigations.

a) Routine investigations

- CBC
- Liver functions AST, ALT.
- Renal functions Urea, creatinine.
- Coagulation profile.
- HbA1c.
- Urine analysis.

b) Serum CLP test procedure

Venous samples were collected and left to clot for 30 minutes then serum was separated by centrifugation. Serum was stored in - 80oc until analysis was performed by enzyme linked immunosorbent assay (ELISA).

4. Follow up of the cases with blood pressure measurement, lab investigations, doppler ultrasound till delivery to detect progression, complications and the outcome of pregnancies in relation to calprotectin level and timing of detection of preeclampsia.

Statistical analysis of the data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were

1. F-test (ANOVA) For normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons
2. Kruskal Wallis test.

For abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons.

RESULTS

A total of 60 pregnant women participated in the study after applying inclusion and exclusion criteria. The overall

incidence of preeclampsia in the study was 10%, while the incidence of Gestational hypertension was 15%.

As regard serum calprotectin , there was no statistically significant difference between preeclamptic and non preeclamptic groups (p= 0.962) (Table 1-4).

Regarding mean arterial blood pressure, it was higher in preeclampsia group than non preeclampsia groups at 24, 28, 32 and 34 weeks of gestation (p<0.001).

As regard urinary protein creatinine ratio, there was statistically significant difference between preeclampsia and non preeclampsia groups at 24, 28, 32 and 36 weeks of gestation (<0.001).

DISCUSSION

Calprotectin is a cytosolic protein, predominantly found in neutrophil cells. It is a zinc- and calcium-binding protein belonging to the S-100 family.

Table 1: The American College of Obstetricians and Gynaecologists (ACOG) has established diagnostic standards for preeclampsia[3]:

• Blood pressure	• Systolic blood pressure of at least 140mm Hg or diastolic blood pressure of at least 90 mm Hg on two separate times, spaced at least four hours apart, after 20 weeks of pregnancy in a woman whose blood pressure was previously normal
	• Severe hypertension can be identified within minutes if the systolic or diastolic blood pressure is greater than or equivalent to 160 or 110 mm Hg, respectively. This allows for the prompt initiation of antihypertensive medication
• And proteinuria	• A 24-hour urine sample of at least 300mg, or this quantity extrapolated from a timed collection, or
	• A protein to creatinine ratio of at least 0.3.
	• Dipstick reading of 2+ used only if other techniques not offered.
Or in the non appearance of proteinuria, (proteinuria is not an essential in preeclampsia), new-onset hypertension with the new onset of any of the following:	
• Thrombocytopenia	• Platelet count is less than 100,000/microliter.
• Renal insufficiency	• Serum creatinine concentration more than 1.1mg/dl, or :
	• A If there are no other renal disorders present, a doubling of the serum creatinine levels would occur.
• Impaired liver function	• Doubled the average levels of liver transaminases in the blood.
• Pulmonary edema	
• A new headache that is not relieved by medication and that is not explained by other diseases or visual signs.	

Table 2: Comparison between the three studied groups according to Mean Blood pressure:

Mean Blood pressure (mmHg)	Preeclampsia (n=6)	Gestational HTN (n=9)	Normal (n=45)	F	p
20 weeks					
Min.–Max.	90.00–106.7	90.00–106.7	76.67–106.7		
Mean±SD.	99.45±5.74	96.67±6.87	94.00±6.34	2.322	0.107
Median (IQR)	100.0(96.67–103.3)	96.67(90.0–103.3)	94.43(90.0–96.67)		
24 weeks					
Min.–Max.	96.83–110.17	93.33–113.3	83.33–106.7		
Mean±SD.	105.2±5.06	101.5±6.03	94.00±6.26	8.539*	0.001*
Median (IQR)	105.2(103.5–110.2)	100.0(96.67–103.3)	93.33(90.0–96.67)		
Sig. bet. grps.		p_1=0.998, p_2=0.015*, p_3=0.004*			
28 weeks					
Min.–Max.	106.7–113.3	93.33–113.3	80.33–106.7		
Mean±SD.	108.3±2.79	103.7±5.88	94.05±6.26	18.573*	<0.001*
Median (IQR)	106.7(106.7–110.0)	103.3(103.3–106.7)	93.41(90.0–96.67)		
Sig. bet. grps.		p_1=0.297, p_2=<0.001*, p_3=0.001*			
32 weeks					
Min.–Max.	106.7–116.7	100.0–113.3	80.00–107.3		
Mean±SD.	111.1±3.44	107.4±3.64	94.07±5.52	35.924*	<0.001*
Median (IQR)	110.0(110.0–113.3)	106.7(106.7–110.0)	94.21(93.33 – 100.0)		
Sig. bet. grps.		p_1=0.365, p_2<0.001*, p_3<0.001*			
34 weeks					
Min.–Max.	116.7–126.7	106.7–116.7	83.33–106.2		
Mean±SD.	118.3±4.08	111.9±4.44	95.24 ± 5.10	75.646*	<0.001*
Median (IQR)	116.7(116.7–116.7)	113.3(106.7–116.7)	94.67(96.67–100.0)		
Sig. bet. grps.		p_1=0.041*, p_2<0.001*, p_3<0.001*			

IQR: Inter quartile range; SD: Standard deviation; F: F for one way ANOVA test, pairwise comparison bet. each 2 groups was done using post hoc test (Tukey); p: p value for comparing between the three studied groups; p_1: p value for comparing between preeclampsia and gestational HTN; p_2: p value for comparing between preeclampsia and normal; p_3: p value for comparing between gestational HTN and normal; *: Statistically significant at $p \leq 0.05$.

Table 3: Comparison between the three studied groups according to urinary protein creatinine ratio PCR:

PCR	Preeclampsia (*n*= 6)	Gestational HTN (*n*= 9)	Normal (*n*= 45)	*H*	*P*
24 weeks					
Min.–Max.	0.10–0.40	0.10–0.20	0.10–0.20		
Mean±SD.	0.25±0.12	0.13±0.05	0.11±0.03	16.189*	<0.001*
Median (IQR)	0.30(0.10–0.30)	0.10(0.10–0.20)	0.10 (0.10–0.10)		
Sig. bet. grps.		p_1=0.036*, p_2<0.001*, p_3=0.111			
28 weeks					
Min.–Max.	0.20–1.20	0.10–0.20	0.10–0.20		
Mean±SD.	0.57±0.40	0.14±0.05	0.13±0.05	19.977*	<0.001*
Median (IQR)	0.40 (0.30–0.90)	0.10(0.10–0.20)	0.10(0.10–0.20)		
Sig. bet. grps.		p_1=0.002*, p_2<0.001*, p_3=0.435			
32 weeks					
Min.–Max.	0.40–2.10	0.10–0.20	0.10–0.20		
Mean±SD.	1.08±0.76	0.17±0.05	0.14±0.05	22.109*	<0.001*
Median (IQR)	0.75(0.50–2.0)	0.20(0.10 – 0.20)	0.10(0.10 – 0.20)		
Sig. bet. grps.		p_1=0.005*, p_2<0.001*, p_3=0.141			
34 weeks					
Min.–Max.	0.50–2.90	0.10–0.20	0.10–1.20		
Mean±SD.	1.63±0.92	0.18±0.04	0.17±0.16	20.629*	<0.001*
Median (IQR)	1.90 (0.60–2.0)	0.20(0.20–0.20)	0.10(0.10–0.20)		
Sig. bet. grps.		p_1=0.006*, p_2<0.001*, p_3=0.174			

IQR: Inter quartile range; SD: Standard deviation; *F*: *F* for one way ANOVA test, pairwise comparison bet. each 2 groups was done using post hoc test (Tukey); *p: p* value for comparing between the three studied groups; p_1*: p* value for comparing between preeclampsia and Gestational HTN; p_2: *p* value for comparing between preeclampsia and normal; p_3*: p* value for comparing between Gestational HTN and normal; *: Statistically significant at $p \leq 0.05$.

Table 4: Comparison between the three studied groups according to serum calprotectin:

Serum calprotectin *n*g/mL	Preeclampsia (*n*=6)	Gestational HTN (*n*= 9)	Normal (*n*= 45)	*H*	*p*
Min.–Max.	1055–2440	1212–2000	835–3700		
Mean±SD.	1672.5±560.2	1618.9±321.5	1661.6±590.5	0.077	0.962
Median (IQR)	1660(1070–2150)	1630.0(1318–1980)	1600(1307–1900)		

IQR: Inter quartile range; SD: Standard deviation; H: H for Kruskal Wallis test; *p*: *p* value for comparing between the three studied groups.

Calprotectin is released by activated neutrophils. Elevated levels of calprotectin in plasma have been found in inflammatory states, autoimmune diseases, and infections. As well as being a marker of inflammation, calprotectin has antimicrobial, cytotoxic, and cytokine-like effects, and is proposed to be an important mediator with regulatory functions in inflammatory reactions.

Preeclampsia is a pregnancy-induced syndrome, characterized by hypertension and proteinuria, affecting 3% to 5% of pregnancies. Maternal endothelial dysfunction, inflammation, and leukocyte activation are part of the pathophysiology and circulating factors originating from the uteroplacental circulation are probably essential in the clinical development of preeclampsia.

In this prospective observational study 60 pregnant females at gestational age 14th to 16th weeks attending obstetrics clinic of ELShatby university hospital participated in the study after applying inclusion and exclusion criteria.

The association of CLP in hypertensive diseases has gained great attention in recent years and many studies have investigated the role of calprotectin specifically in preeclampsia.

Li *et al.*, for example, found mean levels of serum Calprotectin in Preeclamptic patients to be significantly higher compared to healthy controls (mean 2656±1724 µg/l and 1877±905 µg/l respectively), (p<0.05).

Similar results were also found by Börekci *et al.,* demonstrating a mean of 1677.4±1222.0 µg/l vs. 772.1±451.4µg/l in Preeclamptic patients and healthy controls respectively (p<0.05).

Moreover, Feng *et al.,* demonstrated a serum CLP level of 751±258 µg/l in mild Preeclamptic patients as compared to 1012±699 µg/l in severe PET. Many other studies showed a totally different range of serum CLP level in preeclamptic patients, all of which presented a higher serum CLP level in PET patients than in healthy control.

As opposed to these studies, however, our study revealed no statistically significant difference between preeclamptic, gestational hypertensive and normotensive groups (1672.5±560.2 vs 1618.9±321.5 vs 1661.6±590.5 respectively) (p= 0.962).

Bayrakci *et al.,* suggested a compelling explanation: that serum CLP might have been broken down at the site of inflammation (in vivo) or during storage (in *vitro*). Similarly, Hoskin *et al.,* reported that vigorous proteolysis of oxidized Calprotectin is bound to occur both at the site of inflammation or during storage of clinical samples. They warned that the increased susceptibility to proteolysis during storage or at the inflammation site should be considered when interpreting Calprotectin levels measured by ELISA as it will underestimate the true inflammation level.

Edwards *et al.,* and Stephan *et al.,* found that proteolysis of CLP may occur in vivo rather than during sample handling and storage.

Systemic inflammation and leucocyte activation/ degranulation have been already proposed as potential pathways which contribute to the pathogenesis of preeclampsia.

Interestingly, in 2022, Teagan *et al.,* conducted another study reporting the degradation of CLP and the liberation of 6 specific peptides from oxidized CLP in the airways of children with Cystic Fibrosis. Four of the six peptides correlated with the neutrophil derived enzyme MPO. These interesting findings lead the authors to steer away from the idea of using intact CLP as a biomarker of inflammation and rather suggested the use of the resulting peptides as a diagnostic biomarker that reflects neutrophil numbers.

Teagan *et al*., highlighted that the underestimated level of CLP is not restricted to their cystic fibrosis patients only, but can also occur in any disease where neutrophils release CLP and huge amounts of oxidants.

Other than the possibility of in-vivo proteolysis, there are many pre-analytical factors play an important role in the determination of the serum CLP level. These factors include but are not confined to the presence/ absence of anticoagulants, sample storage temperature and duration.

The absence of ethylenediamine tetraacetic acid (EDTA) in serum samples makes CLP in serum samples less stable than that in EDTA-plasma samples. As we already mentioned before, CLP is a calcium binding protein and because calcium is released from monocytes by a calcium-dependent activation of an enzyme named protein kinase C, EDTA's calcium binding method of anticoagulation, inhibits the release of CLP from monocytes and thus provides a stabilizing effect on CLP levels. Since coagulation is necessary for obtaining serum, this stabilizing effect isn't present in serum samples and therefore CLP levels measured in serum may provide misleading results.

CONCLUSION

Our study revealed no statistically significant difference between preeclamptic, gestational hypertensive and normotensive groups. The most important factor being its susceptibility to proteolysis that may occur either in vivo due to the uncontrolled MPO derived oxidative stress or pre-analysis: during sample handling and storage. Either way, a consequent unreliable and underestimated CLP levels when measured by ELISA occurs. This stands as a huge limitation in the use of CLP as a biomarker of neutrophil-mediated inflammation. Further studies are required to explore the stability of CLP under long storage conditions. Also, accurate understanding of the causes of in vivo CLP degradation and the production of its resultant peptides is crucial to understand the neutrophil-induced oxidative stress and tissue damage.

CONFLICT OF INTERESTS

There are no conflict of interests.

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