EVALUATION OF MATERNAL SERUM ENDOGLIN IN PREECLAMPSIA AND IN NORMOTENSIVE PREGNANT FEMALES

Samar A. Ibrahim[1*], Alaa S. Hassanin[2], Helmy M. Elsyad[2], Amani M. Abdel Ghani[2] and Salma A. Nassar[2]

Department of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University, Cairo, Egypt

Corresponding author
Samar A. Ibrahim.
Mobile: + (2) 01092947650
E.mail:
zamilsamar@yahoo.com

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ABSTRACT

Background*: Preeclampsia is characterized by an imbalance in angiogenic factor, including soluble endoglin. Serum soluble endoglin levels were significantly different in patient with preeclampsia than in healthy pregnancy.*

Aim of the work*: Evaluation of the increased level of serum soluble endoglin in preeclampsia and normotensive pregnant females.*

Patients and Methods*: Forty pregnant female of at least twenty weeks of gestation were included and divided into two equal groups; preeclamptic and non preeclamptic group. 5ml of blood were collected by venipuncture into test tube without anticoagulant. Plasma endoglin was assayed by one-step sandwich enzyme immunoassay using monoclonal antibodies to human endoglin using kits.*

Results*: preeclampsia group had higher endoglin level compared to normal one with statistically highly significant difference 18.52 ± 9.54 versus 2.2 ± 1.4 (p= 0.000) and elevated serum soluble endoglin showed a significant +ve correlation (r=0.523, P=0.016) with a risk of pre-eclampsia. With the highest positive predictive and lowest negative predictive values, a cutoff point of 6.26500 ng/ml had the best sensitivity and specificity.*

Conclusion*: Serum soluble endoglin has a remarkable accuracy for diagnosis of preeclampsia.*

Keywords*: Serum soluble endoglin, preeclampsia*

INTRODUCTION:

Preeclampsia is a pregnancy-related illness identified by high blood pressure and proteinuria after 20 weeks of pregnancy that affects 2 to 8% of all pregnancies globally[(1)].

It is the leading cause of morbidity and mortality in both mothers and fetuses. It contributes to major proportion of maternal death up to 16% in developed countries[(2)].

It is a multi - system condition throughout the 2nd and 3rd trimesters of pregnancy.After twenty weeks of pregnancy, it is identified by blood pressure greater than or equal to 140/90 mmHg, a rise in systolic blood pressure greater than thirty mmHg, or a rise in diastolic blood pressure greater than fifteen mmHg, and albuminuria greater than or equal to three hundred mg/twenty four hours [(3)].

Various risk factors and preventive methods have been tested still there are no definitive preventive methods [(4)].

Preeclampsia is identified as high blood pressure with thrombocytopenia (platelet count < 100.000/ml), incapacitated hepatic function (increased hepatic transaminases to double the standard level), impaired kidney function (serum creatinine > 1.1 mg/dl or doubling of serum creatinine in the lack of all other kidney impairment), lung edema, as

well as new incidence of brain or eye manifestations in the lack of albuminuria[5].

Although new researches into the pathogenesis of preeclampsia, the disease continues to be a challenge, without effective treatment and prevention restricted to delivery to cease the pregnancy and the disease. Reduced placental circulation, mainly due to aberrant trophoblastic invasion, with subsequent dilatory remodeling of maternal arteries perfusing the placenta, preceding and resulting in the clinical signs of preeclampsia, according to a current model of the pathophysiology of preeclampsia. Several variables, such as female constitutional characteristics, antiangiogenic factors, and inflammatory activation, have already been implicated in the initiation and progression of preeclampsia[6].

Poor placentation has been hypothesized as a fundamental factor in the pathophysiology of preeclampsia. Endothelial dysfunction is thought to be a main mechanism in the pathophysiology of preeclampsia. An ischemic placenta produces soluble substances into the vascular system, which have been linked to endothelial dysfunction and preeclamptic manifestations. Determination of soluble endoglin could also be utilised as a reliable screening method for high-risk women who are likely to develop preeclampsia before it manifests clinically, ultimately improving pregnancy outcomes[7].

PATIENTS AND METHODS:

Forty pregnant female of at least twenty weeks of gestation were included and divided into two equal groups; preeclamptic and non preeclamptic group.

Study type:

A case control study.

Study place:

Ain Shams University Maternity Hospital.

Study period:

October 2020 till June 2021.

Inclusion criteria

Women aged from 18:35 years with gestational age > 20 weeks, singleton pregnancy and body mass index <30.

Exclusion criteria:

Women with preexisting medical conditions like deep venous thrombosis, hypercoagulable state, known thrombophilia, diabetic, chronic hypertension, cardiovascular, autoimmune, renal, hepatic diseases, multiple pregnancy and/or congenital fetal malformation.

Study procedures:

The study started after approval of the research ethics committee, Faculty of Medicine, Ain Shams University. Informed consent was taken from all participants. Data confidentiality was maintained.

5ml blood were collected by venipuncture into test tube without anticoagulant, clotting was allowed, Serum was separated by centrifugation at room temperature for 20 minute at 2000 rpm at laboratory of obstetrics and gynecology hospital. We did not centrifuge before complete clotting. Blood samples then were transported to be frozen at -20°C at laboratory of Microbiology and Immunology at faculty of medicine Ain Shams University for testing. Plasma endoglin was assayed by one-step sandwich enzyme immunoassay using monoclonal antibodies to human endoglin using kits; this kit was used to assay soluble endoglin in the sample of human´s serum.

The primary outcome was the association between serum soluble endoglin level and preeclampsia.

Secondary outcome parameters were correlation between level of serum endoglin in preeclampsia and normotensive pregnant ones and correlation between body weight and preeclampsia.

Statistical Analysis:

Data were tabulated and statistically analyzed using SPSS, version 20 (SPSS Inc., Chicago, IL). Independent Mann Whitney test and Kruskal-Wallis Test were used for comparing quatitative variables between groups. Qualitative data were expressed as frequancies (n) and percentage (%). Pearson correlation coefficient was used to correlate between quantitative variables. P-value ≤ 0.05 was considered significant.

RESULTS:

The basic demographics of the study groups did not differ significantly at the time of recruitment. Urine albumin, ALT, AST, Platelet count, Creatinine, and Uric acid showed significant differences across the groups. (See Table 1)

Table 1: Comparison between both groups as regard clinical characteristics / routine investigations

Variables		Group A	Group B	Test	P value
Result #		2.5±1.8 (0.5-7.6)	19.1±9.4 (10-39.3)	7.557	.000*
O.D #		0.3±0.2 (0-0.7)	1.1±0.3 (0.8-1.9)	9.878	.000*
Age #(in years)		28.9±6.2 (19-41)	30.3±6.9 (20-45)	.681	.500
Parity †	P2	6(28.6)	4(21.1)	1.135	.833
	P3	4(19)	3(15.8)		
	P4	2(9.5)	1(5.3)		
	Primi	9(42.9)	11(57.9)		
Gestation age #(in weeks)		38.2±2.3 (33-42)	36.6±1.7 (32-38)	2.599	.013*
Systolic blood pressure #(mmHg)		110.2±23 (90-180)	145.3±19.5 (120-180)	5.155	.000*
Diastolic blood pressure #(mmHg)		74.8±7.5 (70-100)	91.6±12.5 (70-110)	5.101	.000*
Proteinuria †	0	10(47.6)	1(5.3)	20.483	.000*
	1	8(38.1)	3(15.8)		
	2	3(14.3)	6(31.6)		
	3	0(0)	9(47.4)		
HB #		10.3±1.1 (7.8-12)	10.2±1.3 (7.8-12)	.068	.946
Creatinine # mg/dl		0.7±0.1 (0.5-0.9)	0.8±0.2 (0.5-1.3)	1.519	.137
Liver enzymes † u/l	Elevated	2(9.5)	5(26.3)	--	.226
	Normal	19(90.5)	14(73.7)		
Body weight #(kilograms)		85.9±7.2 (77-104)	94.9±8.4 (82-112)	3.670	.001*
Height #(cm)		158.1±5.2 (147-170)	165.8±6.7 (158-180)	4.114	.000*

Preeclampsia group had higher endoglin level compared to normal group with statistically highly significant difference in between by using Mann Whitney test. The result of control pregnancy was (2.2±1.4). The result of study group was (18.52±9.54). Moreover, elevated serum soluble endoglin showed a significant positive correlation (r=0.523, P=0.016) with a risk of pre-eclampsia. (Table 2 and 3)

Table 2: Soluble endoglin level in both groups, Comparison between both groups according to result and O.D

Soluble Endoglin level in both groups				
Variables		N (%) / mean ± SD (min – max) / median (IQR)		
groups	Control group	20(50)		
	Study group	20(50)		
Result	Mean ± SD	10.36±10.66(0.5-39.3)		
	Median(IQR)	6.27(2.51-13.5)		
Comparison between both groups according to Result and O.D				
	Control group mean ± SD (min – max) / median (IQR)	Study group mean ± SD (min – max) / median (IQR)	Kruskal-Wallis Test	P
Result	2.2±1.4(0.5-4.9) 2.51(0.85-2.76)	18.52±9.54(7.63-39.3) 13.5(13.38-25.85)	32.634	.000*
O.D	0.28±0.19(0.04-0.61) 0.33(0.06-0.41)	1.06±0.29(0.72-1.89) 0.98(0.87-1.2)	32.537	.000*
	Independent Mann Whitney test			

Table 3: Correlation between results and O.D in all females

O.D		Control group result	Study group result
O.D	Pearson Correlation	.979	.953
	Sig. (2-tailed)	.000*	.000*

With the highest positive predictive and lowest negative predictive values, the serum soluble endoglin level of 6.26500 ng/ml had the best sensitivity and specificity (Table 4).

Table 4: Sensitivity, specificity and accuracy for serum endoglin

Test	Sensitivity	Specificity	Positive Predictive value	Negative predictive value
Result	100%	100%	100%	100%
O.D	100%	100%	100%	100%

DISCUSSION:

Current study agreed with multiple previous studies; sEng concentrations were three-five- and ten-fold greater in patients with moderate preeclampsia, severe preeclampsia, and HELLP syndrome, respectively, compared to gestational age–matched preterm controls in the current investigation, according to **Venkatesha and his colleagues** [8].

Levine and his colleagues stated that rising circulating levels of soluble endoglin herald the onset of preeclampsia. Within the Calcium for Preeclampsia Prevention trial, they conducted a nested case–control investigation of healthy nulliparous women. All 72 women with preterm preeclampsia (37 weeks) were included in the study, as well as 480 women who were randomly chosen — 120 women with preeclampsia at term (37 weeks), 120 women with gestational hypertension, 120 normotensive women who delivered small-for-gestational-age infants, and 120 normotensive controls who delivered infants who were not small-for-gestational-age infants [9].

According to **Robinson and Johnson**, soluble endoglin levels are higher in second-trimester maternal serum in patients who are likely to develop severe preeclampsia. The enzyme-linked immunosorbent assay was used to analyse single second-trimester serum samples from healthy, nonsmoking

women who developed severe preeclampsia (n = 48) or healthy nonsmoking women who had a normal pregnancy (n = 56). Patients with severe preeclampsia exhibited higher sEng levels than those who had a normal pregnancy (6.19 2.1 vs 5.00 1.0 ng/mL, P =.02) [(10)].

Gu and his colleagues stated that PE trophoblast cells (TCs) produce more sEng than normal TCs. Lowered oxygen conditions promote sEng productions by PE TCs. More glycosylated sEng is present in PE placentas. TCs were cultivated under regular (5 percent CO2/air) and reduced (2 percent O2/5 percent CO2/93 percent N2) oxygen conditions from normal and PE placentas [(11)].

According to **Ali and Mohammed**, preeclamptic women had greater endoglin levels than normal moms, with a statistically significant difference between the two groups. This study comprised 50 pregnant women who were in labour at the time of the study; 25 had a normal pregnancy and 25 had preeclampsia. Each case's maternal serum was obtained after delivery and sent to a lab for endoglin testing [(12)].

The median (25th275th percentile) plasma sEng levels (ng/ml) were significantly higher in women who developed preeclampsia (30.212.7, 55.7) and gestational HTN (6.24.5, 14.0) compared to women who did not have hypertension (4.83.5, 7.1; p, 0.0001, and p= 0.04 respectively) according to **Rana and her colleagues**. This study included data from all women presenting at 34 weeks for preeclampsia evaluation with singleton pregnancies (July 2009-October 2010), and sEng levels were tested at presentation. sEng levels (ng/ml) were considerably higher in individuals who had negative outcomes compared to those who did not (32.3 18.1, 55.8 versus 4.83.2, 8.6, p0.0001). [(13)].

Rana and her colleagues agreed with the findings of the present study but used a different cut-off number. Using a cut-off of 12 ng/ml for sEng, they found that 107 (62.9%) of the individuals were at or below the cut-off, whereas 63 (37.1%) were over. With a sensitivity of 80.4 percent, a specificity of 88.6 percent, a PPV of 77.6 percent, an NPV of 90.2 percent, a positive LR of 7.1, and a negative LR of 0.2, this cut-off exhibited great diagnostic accuracy for bad outcomes [(13)].

According to **Lai and his colleagues**, screening by maternal features and sEng at 30–33 weeks can detect the majority of pregnancies that will have PE. The PE group had a substantially higher median sEng Mom (1.39, IQR 0.94–2.18) than the controls (0.95, IQR 0.77–1.19) at 30–33 weeks, although there was no significant difference between the groups at 11–13 weeks [(15)].

The areas under the ROC and the detection rates of intermediate and late-PE for false-positive rates of 5 and 10% in screening by maternal features and third-trimester sEng, according to **Lai and his colleagues**. At a false positive rate of 10%, the predicted detection rates of intermediate- and late-PE were 64.3 and 50.0 percent, respectively, in screening for PE using a combination of maternal features and third-trimester sEng [(15)].

According to **Abd El-Dayem and colleagues**, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC) for women with preeclampsia were 90 percent, 90 percent, 94.74 percent, 81.82 percent, and 0.984 percent, respectively. The accuracy was 90 percent, and the cut off value was 24 ng/ml [(16)].

Gaber and his colleagues investigated soluble endoglin as a potential novel marker for predicting preeclampsia in early pregnancy. Based on the ROC curve, they found that sEng can distinguish preeclamptic

from normal pregnancies. It scored a 0.962 on the AUC scale. The sensitivity was 94.4 percent, the specificity was 87.5 percent, and the accuracy was 89.5 percent at a cut-off value of 7 ng/ml [(17)].

Finally, using the ROC curve for sEng, **Lee and his colleagues** discovered that a serum level of 21.1 ng/mL had the best sensitivity and specificity when compared to PPV and NPV (90 percent, 83 percent, 84 percent, and 89 percent, respectively) in distinguishing women with preeclampsia from those with normal pregnancy. The ROC curve's area under the curve was 0.924[(18)].

Conclusion

Serum soluble endoglin has a remarkable accuracy for diagnosis of preeclampsia.

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Conflict of interest: None declared

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الإرتباط بين نسبة الإندوجلين بالدم ومعدل حدوث تسمم الحمل

سمر على محمد ابراهيم[1] , آلاء السيد حسانين[2] , حلمى مطاوع السيد[2] , أمانى محمد عبدالغنى[2] , سلمى أشرف نصار[2]

نبذة مختصرة :تتميز مقدمات ارتفاع ضغط الدم للحامل (تسمم الحمل) بخلل فى عامل تكوين الاوعية الدموية , بما فى ذلك الإندوجلين القابل للذوبان . كانت مستويات الإندوجلين القابلة للذوبان فى المصل مختلفة بشكل كبير فى المريضات المصابات بمقدمات تسمم الحمل مقارنة بالحمل الصحى .

الهدف من العمل :تقييم زيادة مستوى الإندوجلين القابل للذوبان فى المصل فى مقدمات تسمم الحمل والحوامل سويه الضغط .

طريقة الدراسة :تم تضمين مجموعة 40 امرأة حامل بعد 20 اسبوعاً من الحمل على الأقل وتم تقسيمهن إلى مجموعتين متساويتين , مجموعة مقدمات تسمم الحمل ومجموعة الحمل الطبيعى .

تم جمع (5 مجم) من الدم عن طريق بذل الوريد فى أمبوب اختبار بدون مضاد للتخثر , تم تقييم نسبة الإندوجلين فى البلازما (تم فصل المصل بواسطة الفصل المركزى فى درجة حرارة الغرفة) حيث لا يتم الفصل المركزى قبل حدوث تجلط كامل للعينة لكى تخزن فى درجة حرارة (- 20) درجة مئوية .

النتائج :كان لدى مجموعة مقدمات تسمم الحمل مستوى إندوجلين أعلى مقارنة بالمجموعة العادية مع اختلاف معتد به إحصائياً 18.52 ± 9.54 مقابل 2.2 ± 1.4 (P = 0.000) وأظهر إندوجلين عالى الذوبان فى المصل ارتباط إيجابى معنوى (r = 0.523 , P = 0.016) مع خطر تسمم الحمل . نقطة القطع 6.26500 نانوغرام / مل لديها أفضل حساسية وخصوصية مع أعلى قيمة تنبؤية إيجابية وأقل قيمة تنبؤية سلبية .

الخلاصة :الإندوجلين القابل للذوبان فى الدم لديه دقة ملحوظة لتشخيص تسمم الحمل .