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Evaluation of Serum Galectin- 3 Levels in Preeclampsia at Term

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ABSTRACT

Background

Pre-eclampsia is a disorder of vascular endothelial dysfunction and vasospasm that occurs after 20 weeks of pregnancy and may occur up to 4–6 weeks after pregnancy. It is defined clinically by hypertension and proteinuria with or without pathological edema. Galectin-3 is expressed in all types of immune cells and organs in human tissues and plays an important role in many biological processes such as inflammatory responses, fibroids, intercellular adhesion, angiogenesis, apoptosis and cell differentiation.

Aim of study

To evaluate Galectin-3 level in pre-eclampsia and to determine the association with severity of pre-eclampsia.

Patients and methods

A case-control study was conducted in the department of obstetrics and gynecology at Azadi Teaching Hospital / Kirkuk/ Iraq. The duration of study was eight months from 1st of February till 1st of October 2021.The study involved 90 patients, 60 preeclamptic women, and 30 (control group) with gestational age (37- 40). Patients were admitted to the hospital for following up their blood pressure, urine test for albumin, renal function test, liver function test were done, between 37-40 weeks gestational age of the pregnancy.

Results

Galectin-3 was significantly higher among pregnant women with severe preeclampsia in comparison to mild pre-eclampsia and control groups (p=0.0001), while no significant correlation in the mean Galectin-3 between normal and mild preeclampsia (P=0.92).

Conclusion: Serum Galectin- 3 is a marker for diagnosis of pre-eclampsia and its severity.

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Introduction:

Hypertension disorders in pregnancy affect 10% of pregnant. Preeclampsia is a widespread disease of vascular endothelial dysfunction and vasospasm, which occurs after 20 weeks of pregnancy and can be presented up to 4–6 weeks after pregnancy[1].

In normal pregnancy, the myometrial and decidual vasculature of the placental implant site is transformed so that the terminal part of the spiral arteriole is large and wide open, resulting in a high-capacity and low-resistance system that provides the best exchange of maternal and fetal nutrients and oxygen. However, in pre-eclampsia, shallow placental formation, and spiral artery remodeling at the beginning of pregnancy, weeks to months before the clinical manifestation of the disease, result in suboptimal blood flow in the uteroplacental flow of the blood and relatively trophoblastic tissue hypoxia[2]. Exaggerated oxidative stress occurs in the placenta, affecting the villous angiogenesis. As pregnancy progresses, pathologic placentas secrete more and more antiangiogenic factors (sFlt-1 soluble fms-like tyrosine kinase-1), bind to vascular endothelial growth factors (VEGFs) and placenta growth factors (PlGFs), leading to widespread maternal vascular inflammation, endothelial dysfunction, hypertension, proteinuria, and other clinical manifestations of preeclampsia [1].

Galectin-3 is a family of β-galactoside-binding lectins with ≥1 evolutionary conserved carbohydrate-recognition domain, expressed in human tissues, including epithelial cells, endothelial cells, and immune cells, and plays an important role in numerous biological processes such as inflammation, fibrosis, intercellular adhesion, angiogenic, cell differentiation, and apoptosis[3].

The role of galectin-3 during pregnancy has not been well explained. It is expressed on the surface of trophoblast cells and its

distribution in normal trophoblasts, as well as in malignant trophoblasts in gestational trophoblastic disease is well known[4]. Experimental studies in the human placental cell line BeWo have confirmed that galectin-3 is one of the factors induced by hypoxia[5].

The aim of this research is to evaluate serum Galectin-3 level in pre-eclampsia and to determine the association with pre-eclampsia and its severity.

PATIENTS AND METHODS

Study design and setting:

A case-control study was conducted in the department of obstetrics and gynecology at Azadi Teaching Hospital / Kirkuk/ Iraq, from 1st of February till 1st of October 2021. The study proposal was accepted by the scientific council of obstetrics and gynecology/Iraqi Board for medical specializations.

The study involved 90 patients, 60 women with pre-eclampsia, 30 women normotensive pregnancy as a (control group), these pregnant women who were present the antenatal clinic and Labor word of Department of Obstetrics and Gynecology. All the participants in our study were matched for age and gestational age.

The preeclampsia of pregnant women was defined according to American College of Obstetricians and Gynecologists (ACOG) by the presence of hypertension and proteinuria or no proteinuria, but with new incident hypertension with either thrombocytopenia (platelets <100 x 109/L), or renal problem (serum creatinine >1.1 mg/dl) or liver dysfunction (abnormal liver enzymes) or pulmonary edema or headache or visual symptoms. The PE is considered mild if blood pressure was less than 160/110 mmHg with proteinuria ≥300 mg in 24 hours, or in dipstick urine 1+(which equal to 0.3g/l). The PE is considered severe if systolic blood pressure was ≥160 mmHg or diastolic blood pressure was ≥110 mmHg or both with protienuria ≥500 mg in 24 hours, or dipstick urine 2+

or more (which equal to 1g/l) where BP measured 2 times 4 hours apart.

Pregnant with preeclampsia were subdivided according to severity of the condition based on American College of obstetricians and gynecologists (ACOG) classification of preeclampsia in to two groups: 30 pregnant patients with mild and 30 pregnant patients with severe preeclampsia.

Inclusion criteria: Maternal age: 16-45 years, gestation: (37- 40) weeks, single viable fetus, acceptance of participant.

Exclusion criteria: Multiple pregnancies. unviable fetus, antepartum hemorrhage, participant refusal, maternal (renal, liver, & cardiac) diseases, maternal autoimmune disease, smoking, RH – ve mother, Preterm gestation, Preterm Prelabor Rupture of Membrane, drug user like (anti-inflammatory, immune modulator chemotherapy) & active labor.

Data collection questionnaire:

The data was collected from pregnant women who received antenatal care or admitted to labor ward for observation at Azadi Teaching Hospital in Kirkuk, by using a planned questionnaire involved the following data:

History was taken for all involved participants. When the pregnant women admitted to labor room, her Blood Pressure (BP) was measured after sitting quietly for 2 to 5 minutes before checking BP, by using suitable size cuff placed on the upper bare arm. Ultrasound was done for viability, gestational age and to exclude twin pregnancy.

Laboratory tests: Test for albumin in urine (dipstick urine test).

Biochemical tests (full blood count, blood urea, serum creatinine, serum uric acid, SGPT, SGOT, alkaline phosphatase, RBS), and Serum Galectin -3 level test. EMC-11S-VUV/VIS spectrophotometer is used for serum galectin-3 measuring.

Statistical analysis:

Version 23 of the statistical package of Social Sciences (SPSS) software was used for data input and

analysis. In socio-demographic descriptive statistics, the mean, standard deviation, minimum, maximum value was used for continuous data. Numbers and percentage values are used to calculate data. The independent sample t and ANOVA test were used to analyze the difference between groups to link continuous variables. The Chi square test is used to associate categorical variables. The Pearson correlation is used to find the correlation between two continuous variables. The ROC is used to identify the cutting value, sensitivity, and specificity of the marker. P0.05 is used as a statistical significance threshold.

RESULTS

There were 90 pregnant women included in this study, in which there were 30 (33.3%) pregnant women with mild preeclampsia, 30 (33.3%) patients with severe preeclampsia, and 30 (33.3%) pregnant women without preeclampsia as control group.

Age of studied groups:

The mean age of all participants was 26.4 ± 6.7 years (range 16 – 45 years). There was no significant difference in the age among studied groups (p=0.5). (Table 1)

Table 1. Age across studied groups

Age of the participants (years)				P value*
Category	**N**	**Mean**	**Std. Deviation**	
Control	30	27.3	6.6	0.49
Mild	30	26.7	6.8	
severe	30	25.2	6.9	
Total	90	26.4	6.7	

*ANOVA test

Participants' characteristics.

The numbers of parity in the studied groups showed no significant difference, in which majority of cases were para 1-4.

There is no significant association between mode of delivery (MOD) and severity of PE.

For albumin, the preeclampsia groups were had urine albumin ranging from 1 plus to 3 pluses and majority of severe preeclampsia cases were had 3 pluses urine albumin, in mild preeclampsia cases were one or two pluses albumin, while all control group cases had no albumin in urine. (Table 2 & Table 3)

Elevated liver function test (LFT) & low platelets count were associated significantly with severity of preeclampsia. While renal function test (RFT) and random blood sugar (RBS) did not show significant difference among studied groups.

Table 2. Participants characteristics

		Control	**Mild**		**Severe**			
		Count	%	Count	%	Count	%	P value
Parity	0	12	20%	8	26.8%	13	43.4%	0.3
	1-4	16	53.4%	20	66.6%	15	50%	
	≥5	2	6.6%	2	6.6%	2	6.6%	
MOD	CS	12	40%	15	50%	19	63.4%	0.19
	VD	18	60%	15	50%	11	36.6%	

MOD: mode of delivery, CS: cesarean section, VD: vaginal delivery

Table 3. Participants characteristics

		Control		**Mild**		**severe**		
		Count	%	Count	%	Count	%	P value
Albumin In urine	0	30	100.0 %	0	0.0%	0	0.0%	**0.001**
	+	0	0.0%	24	80%	1	3.4%	
	++	0	0.0%	6	20%	8	26.6%	
	+++	0	0.0%	0	0.0%	21	70%	
RFT	Normal	30	100%	30	100%	30	100%	
LFT	High AST Level	0	0.0%	4	13.4%	26	86.7%	**0.001**
	Normal	30	100%	26	86.6%	4	13.4%	

CBC	Anemia	3	10.0%	2	6.6%	5	16.8%	**0.005**
	Low platelets	0	0.0%	5	16.8%	10	33.2%	
	Normal	27	90%	23	76.6%	15	50%	
RBS	High	0	0.0%	2	6.6%	5	16.8%	0.053
	Normal	30	100%	28	93.4%	25	83.4%	

RFT: renal function test, LFT: liver function test, CBC: complete blood count, RBS: random blood sugar.

Galectine-3 level.

The mean Galectine-3 level across all participants was 32.7 ± 34.2 (range 2 – 179 ng/ml). The mean Galectine-3 was significantly higher among pregnant women with severe preeclampsia in comparison to other groups (p=0.0001), while the mean Galectine-3 was not significantly higher among pregnant women with mild preeclampsia in comparison to control group (p=0.92). (Table 4).

Table 4. The mean Galectine-3 level across all participants.

Galectin (ng/ml)				P value*
Category	**N**	**Mean(ng/ml)**	**Std. Deviation**	
Control	30	17.29	12.41	**0.0001**
Mild	30	24.50	34.63	
Severe	30	60.65	35.54	
Total	90	32.73	34.21	

*ANOVA test

Identifying the cutoff value for Galectine-3 level between severe preeclampsia and other groups showed that, Galectine-3 Cut off level of ≥ 22 ng/ml was associated with sensitivity 80.77% and specificity 83.61% and correctly classified 82.76% of cases. (Figure 1)

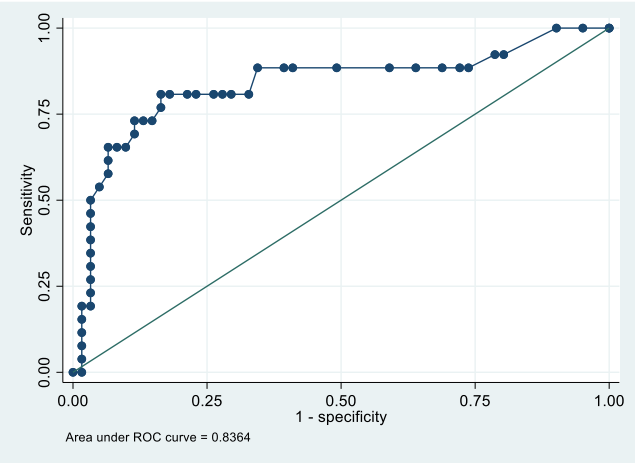

Figure 1. Receiver operating characteristic (ROC) curve for Galectine-3 level between severe preeclampsia and control group.

While identifying the cutoff value for Galectine-3 level between severe preeclampsia and mild preeclampsia showed that, Galectine-3 Cut off level of ≥ 13ng/ml was associated with sensitivity 80.77% and specificity 76.67% and correctly classified 78.57% of cases. (Figure 2)

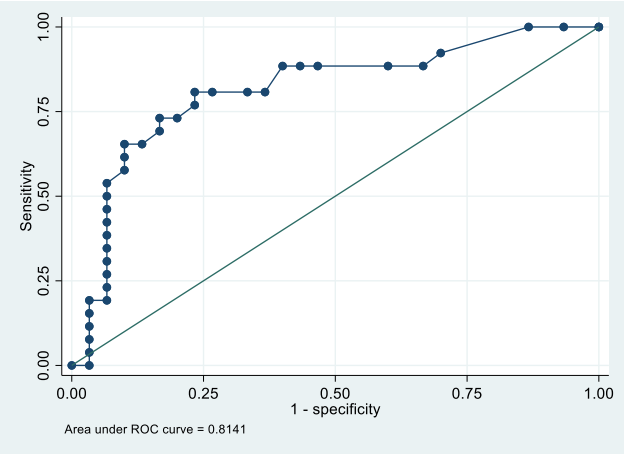

Figure 2. Receiver operating characteristic (ROC) curve for Galectine-3 level between severe and mild preeclampsia.

Factors associated with Galectine-3 level across all patients.

Assessing the factors that associated with Galctine-3 level showed that, there were significant associations between levels of Galctine-3 and increased Albumin and higher liver function test (with higher AST). While other factors did not show significant difference between groups. (Table 5, 6, 7 & 8)

Table 5. Galctine-3 level across Albumin level among all participants.

Galectin				
Albumin	**N**	**Mean (ng/ml)**	**Std. Deviation**	**P value***
0	30	17.36	12.48	**0.001**
1	25	19.23	15.13	
2	14	76.44	41.44	
3	21	54.38	30.44	
Total	90	32.73	34.21	

*ANOVA test

Table 6. Galctine-3 level across MOD among all participants.

Galectin ng/ml				
MOD	**N**	**Mean**	**Std. Deviation**	**P value***
CS	46	36.84	33.81	0.29
VD	44	28.33	34.50	
Total	90	32.73	34.21	

MOD; mode of delivery. CS; caesarean section. VD; vaginal delivery.

*Independent sample t test.

Table 7 Galctine-3 level across LFT among all participants.

Galectin				
LFT	**N**	**Mean (ng/ml)**	**Std. Deviation**	**P value***
High	30	56.96	36.69	**0.001**
Normal	60	19.98	24.911	
Total	90	32.73	34.218	

*Independent sample t test.

Table 8. Galctine-3 level across CBC among all participants.

Galectin				
CBC	**N**	**Mean (ng/ml)**	**Std. Deviation**	**P value***
Anemia	10	26.50	24.981	0.05
Low Platelets	15	52.26	31.246	
Normal	65	29.01	34.933	
Total	90	32.73	34.218	

*ANOVA test

DISCUSSION

Galectin-3 is widely expressed in human tissues including all types of immune cells (Macrophages, Monocytes, Dendritic Cells, Eosinophils, Mass Cells, Natural Killers and T and B Active Cells), epithelium cells, endothelium cells, and sensory neurons. Galectin-3 expression in tissues is more abundant during embryonic development than in adult life. Galectin-3 knockout mice are viable without obvious abnormalities, except for premature senescence[6]. It is expressed on the surface of trophoblast cells as well as in malignant trophoblasts in gestational trophoblastic disease, is well known[7].

Age of the participants:

In our study there was no significant difference in ages among the studies groups, this a against a study by Li et al showed that the maternal age was associated with increased risk of PE, in which, maternal age ≥35 years is associated with early onset PE[8]. Also, a study by Ogawa et al showed that women aged 45 or older had higher risk of preeclampsia[9]. Thus, roll out the bias of age will add more strength to our results. The difference might be explained by difference in the sample size, gestational age, environmental & genetic variation

Urinary albumin level:

This study showed that there was a significant association between level of albumin and severity of PE. This was in line with a study by Begum et al that showed urinary albumin was associated significantly with presence of preeclampsia[10]. However, another study by Duan et al showed that no role for serum albumin in prediction of severity of preeclampsia[11]. This comes in line with fact that serum albumin did not used to assess the severity of preeclampsia.

Mode of Delivery among participants:

Despite higher rate of Cesarean Section (CS) among preeclampsia women in comparison to normal pregnant women, in this study there

was no significant difference among groups. This result is reverse to a study done by Majeed et al in Iraq[12], the rate of CS in their study was much higher (79.7%). This is related to fact that pregnant women with preeclampsia have higher rate of CS due to maternal condition that need speedy delivery to avoid further complication.

The different rate of CS among groups in this study & above mention studies might be explained that the gestational age of pregnant who participate in their study was different.

Liver Function Test & Complete Blood Count

In this study elevated liver function test and low platelet level, were associated significantly with preeclampsia patients and this was comparable to recent study results by Sisti et al that showed the elevated liver enzymes and low platelet is higher among preeclampsia women in comparison to controls[13]. This in fact relate to the pathogenesis of preeclampsia in which it affects multi organs that used as diagnostic criteria for preeclampsia.

Galectine-3 level

The mean Galectine-3 level across all participants was 32.7 ± 34.2 (range 2 – 179). The mean Galectine-3 was significantly higher among pregnant women with severe preeclampsia in comparison to other groups, while the mean Galectine-3 level was not significantly differ among pregnant women with mild preeclampsia in comparison to control group.

This was in line with recent study conducted in Iraq by Sattar et al that showed the preeclampsia group had significantly higher galectin-3 levels than the control group Furthermore, they found that the high galectin-3 also is correlated positively with dyslipidemia[14].

Also, this was in line with Pankiewicz et al study that showed the level of Galectine-3 was significantly higher among preeclampsia group in comparison to control group at delivery[15].

Moreover, a study by Jeschke et al showed that galectin-3 was up-regulated on the membrane of extravillous trophoblast in preeclamptic placentas[16].

A recent study by Ruikar et al showed that there was an increase in the expression Galectin-3 in hypertensive group compared with the normotensive control group, this increase in placental bed may be associated with a systemic inflammatory response in preeclampsia, suggesting role of Galectin-3 in preeclampsia pathogenesis[17].

While there was one a study conducted by Atakul et al showed that no significant difference was observed in Galectin-3 between preeclampsia and control groups[18].This might come from difference in method of detecting the Galectin-3 level. Also, a study by Nikolov et al concluded that serum galectin-3 levels may not be a useful method for prediction of early-onset preeclampsia[19]. And this was differed from our study in which our aim was focusing only at term.

Identifying the cutoff value for Galectine-3 level between severe preeclampsia and other groups showed that, Galectine-3 Cut off level of ≥ 22ng/ml was associated with sensitivity 80.77% and specificity 83.61% and correctly classified 82.76% of cases, while Identifying the cutoff value for Galectine-3 level between severe preeclampsia and mild groups showed that, Galectine-3 Cut off level of ≥ 13ng/ml was associated with sensitivity 80.77% and specificity 76.67% and correctly classified 78.57% of cases. A study done by Gencheva et al that showed the most appropriate cut-off values of Galectin-3 in each case were determined to be as close to 100% sensitivity and 100% specificity as possible and were (≥7.15) ng/ml for gestational hypertension vs. controls; (≥6.25) ng/ml for preeclampsia vs. controls, and (≥7.25) ng/ml for the combined hypertensive group vs. controls[20]. However, the main

difference from this study is they reported that the Galectin-3 levels were significantly lower in the control group compared to both the gestational hypertension group (P=0,022) and to the preeclampsia group (P=0,004).

Assessing the factors that associated with Galctine-3 level showed that, there were significant associations between levels of Galctine-3 and increased Albumin and high LFT. This was against the finding of Gencheva et al study, in which the authors demonstrated no significant difference in Galectin-3 level and above-mentioned factors[20.] This difference might relate to difference in sample size and method used in both studies.

CONCLUSIONS

Based on the result of the study, we concluded the following:

1- Galectin is appropriate marker for diagnosis of severe pre-eclampsia at cutoff level >22ng/ml.

2- Assessing the factors that associated with Galctine-3 level showed that, there were significant associations between levels of Galctine-3 with increased level of Albumin and high LFT (with higher ALT).

3- Assessing the factors that associated with Galctine-3 level showed that, there were non-significant associations between levels of Galctine-3 and mode of delivery and with the results of complete blood count (CBC).

RECOMMENDATIONS

1- Our finding of appreciated role of Galectin-3 as a diagnosis for preeclampsia and its severity needs to be further evaluated in larger, multi center studies before wider clinical application in the management of preeclampsia.

2- A- Further studies are needed to confirm the exact serum profile of Galectin-3 in normal

pregnancy to determine the appropriate screening and monitoring schedule of high-risk women.

B- Future studies with different design including serial measurements of Galectin-3 level to confirm the role of the concerned biomarker in early prediction of PE

3- Further studies with different sample size to confirm exact level of Galectin level in normal pregnancy at early gestational age in the relation to preeclampsia.

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