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The level of maternal serum galectin-1 and galectin -3 levels in pregnancies complicated with preterm prelabour rupture of membrane

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Abstract
Background: Rupture of membranes occurring prior to 37 weeks of gestation. It complicates Approximately 2% of pregnancies, and 40% of these cases result in preterm delivery, contributing significantly to increased neonatal morbidity and mortality.
Objective: To assess the level of maternal serum galectin-1 and galectin -3 levels in pregnancies complicated with preterm prelabour rupture of membrane.
Patients and method: A case control study that carried out in Obstetrics and Gynecology Department at Baghdad Teaching hospital from the first of Jan 2020 to the end of Dec 2020. A sample of 200 pregnant women participated in the study within gestational age (24 -<36+6) weeks.
Results: The level of Galectin-1 was (11763±389) in PROM group and (11443±599) for normal group with highly significant increase in case group than that in normal group (P< 0.001). Galectin-3 was (3112±329) in PROM group and (2711±265) for normal group with highly significant increase in case group than that in normal group (P< 0.001). The validity test of the Galectin-1 to detect the PROM at cutoff value≥11721 and AUC= 0.93 was; Sensitivity (94%), specificity (78%), NPV (90%), PPV (80%) and accuracy was (88%), and the validity test of the Galectin-3 to detect the PROM at cutoff value ≥2990 and AUC= 0.88 was; Sensitivity (89%), specificity (74%), NPV (86%), PPV (76%) and accuracy was (82%).
Conclusion: Significant increase of Galectin-1 and 3 in Premature rupture of membrane than that in normal group (P< 0.001).

Keywords: Preterm prelabour rupture of membrane, galectin-1, galectin -3, pregnancy

Introduction

Preterm premature rupture of membranes is defined as: Rupture of membranes occurring prior to 37 weeks of gestation. It complicates approximately 2% of pregnancies, and 40% of these cases result in preterm delivery, contributing significantly to increased neonatal morbidity and mortality [1]. Cessation of amniotic fluid leakage with restoration of normal amniotic fluid volume may occur in the setting of spontaneous preterm PROM and is associated with favorable outcomes. Among women with preterm PROM, clinically evident intra-amniotic infection occurs in approximately 15–25%, and postpartum infection occurs in approximately 15–20%; the incidence of infection is higher at earlier gestational ages. Abruptio placentae complicates 2–5% of pregnancies with preterm PROM [2].

pPROM: A disease of the fetal membranes

Unlike the placenta, fetal membranes are not involved in transport of nutrients or other materials. One of the major functions of fetal membranes is to protect the fetus during its growth and development in utero. Specifically, the fetal membrane functions to provide mechanical. And immune protection and acts as a barrier for microbial access [3]. This protective role is supported by the biomarkers that are produced by fetal membranes during gestation and parturition. Compromise in the immune and mechanical properties of the fetal membranes allows for microbial invasion from genital tract, activation of host inflammatory response leading to collagenolysis mediated mechanical disruption [4], and membrane weakening predisposing the membranes to pPROM. Abruption associated thrombin, matrix metalloproteinase (MMP) activation and collagenolytic processes have also been reported in fetal membrane weakening and pPROM [5].

Clearly, the dysfunctional status of fetal membranes is more evident in pPROM than sPTB with no ROM. Thus, pPROM is considered as a disease of the fetal membranes and likely a separate entity from sPTB with no ROM [6].

Galectin

Galectins, a family of soluble b-galactoside–binding proteins widely expressed at sites of inflammation, infection, and tumor growth, have emerged as a new class of DAMPs or RAMPs that serve to amplify or resolve inflammatory responses [7].

Gal-1

Gal-1, the first galectin identified, acts typically as a pro-resolving mediator by repressing a number of innate and adaptive immune programs. From a structural standpoint, Gal-1 is composed of two subunits of 14.5 kDa (135 aa) present in a dynamic dimerization equilibrium [7].

Because of an unusual number of six cysteine residues, this lectin is highly sensitive to oxidative inactivation, which limits its biological activity [8].

Thus, sensitivity to Gal-1 is influenced by intrinsic and extrinsic factors, including dimerization equilibrium, redox status, and the regulated activity of glycosyltransferases responsible for creating or hindering specific glycan structures on target cells [8, 9].

Galectin-3

The human Gal-3 gene (LGALS3) spans 17 Kb and contains 6 exons and 5 introns. It has an open reading frame of 750 bp which translates into a protein of 250 amino acids with a Mr of approx. 30,000. As aforementioned, Gal-3 has a unique structure among galectins. The C-terminal half, that is the CRD, is folded into a β-sandwich fashion with a tryptophan core and a non-canonical carbohydrate-binding site that mediates interaction with sugars such as N-acetyllactosamine (its preferential ligand), galactomannans, and polymannan [10]. The glycine- and proline-rich domain is involved in the ability of Gal-3 to oligomerize with other Gal-3 molecules or to establish protein-protein interactions with distinct proteins [1].

Role in pregnancy

Galectin is thought to play a role in creating immune tolerance in pregnancy [12]. Galectin-1 is expressed by the endometrial stromal cells throughout the menstrual cycle, however significantly increases during implantation. Galectin induces the differentiation of dendritic cells towards a phenotype which dampens T helper 1 cells and T helper 17 cells and dampens inflammation via interleukin-10 and interleukin-27 [13]. It also plays a role in the formation and expression of HLA-G in the syncytium. Galectin-1 and galectin-3 are mainly located in the endometrial stroma, fetal membranes, decidua, and trophoblasts. As galectins are highly expressed at the maternal–fetal interface, the dysregulation of the expression of galectins has been associated with obstetrics complications, such as preterm labor, preeclampsia, and fetal growth restriction [14].

Aim of the study

To assess the level of maternal serum galectin-1 and galectin -3 levels in pregnancies complicated with preterm prelabour rupture of membrane.

Patients and method

A case control study that carried out in Obstetrics and Gynecology Department at Baghdad Teaching hospital from the first of Jan 2020 to the end of Dec 2020. A sample of 200 pregnant women participated in the study within gestational age (24 -<36+6) weeks. And divided into 2 groups:

1. 100 patients with Premature rupture of membrane as (case group).
2. 100 normal healthy pregnant ladies as (control group).

Statistical analysis

After the data were entered in a table developed by the researchers, the analysis was done by using the SPSS program, version 23 and for qualitative variables, we used frequencies and percentages, and for the quantitative variables, we used measures of central tendency and dispersion (standard deviation). For the inferential statistics, the tests were used of chi-square test (with a significance of $P \leq 0.05$). Validity test were done to measure the (sensitivity, specificity, NPV, PPV and accuracy of the test.

Results

The level of Galectin-1 was (11763±389) in PROM group and (11443±599) for normal group with highly significant increase in case group than that in normal group ($P< 0.001$). Galectin-3 was (3112±329) in PROM group and (2711±265) for normal group with highly significant increase in case group than that in normal group ($P< 0.001$) (table 1).

Table 1: Level of Galectin 1 and 3 in the studied groups

	PPROM group (n=96)	Normal group (n=96)	p values
Galectin 1 (pg/ml)	11763±389	11443±599	<0.001
Galectin 3 (pg/ml)	3112±329	2711±265	<0.001

The validity test of the Galectin-1 to detect the PROM at cutoff value≥11721 and AUC= 0.93 was; Sensitivity (94%), specificity (78%), NPV (90%), PPV (80%) and accuracy was (88%) (Table 2 and figure 1)

Table 2: Validity test of serum Galectin-1 in PROM

Cutoff value of Galactin-1	Sensitivity	Specificity	NPV	PPV	Accuracy
≥11721	94	78	90	80	88

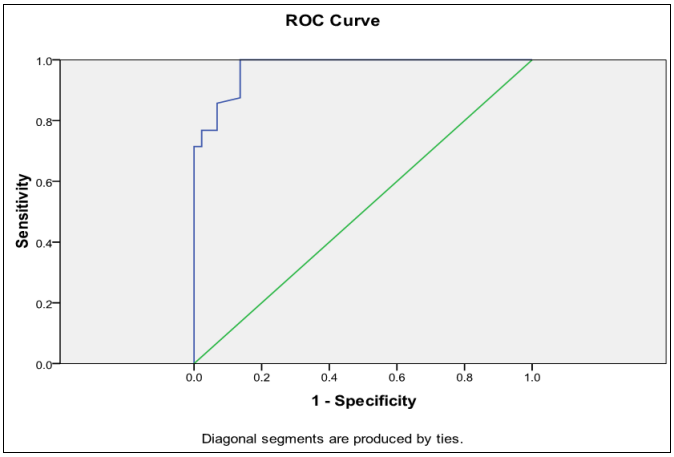

Fig 1: ROC curve for Galectin 1 in PROM (AUC=0.93).

The validity test of the Galectin-3 to detect the PROM at cutoff value ≥2990 and AUC= 0.88 was; Sensitivity (89%), specificity (74%), NPV (86%), PPV (76%) and accuracy was (82%) (Table 3 and figure 2)

Table 3: Validity test of serum Galectin-3 in PROM

Cutoff value of Galectin-3	Sensitivity	Specificity	NPV	PPV	Accuracy
≥2990	89	74	86	76	82

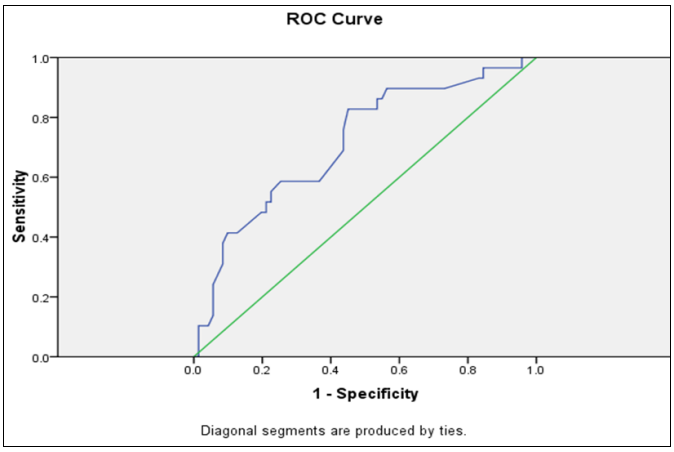

Fig 2: ROC curve for Galectin-3 in PROM (AUC=0.88)

Discussion

A timely and accurate diagnosis of PROM is critical to optimize perinatal outcome and minimize serious complications such as placental abruption and chorioamnionitis [15].

In our study, the main age group were in between (21-30) years in which 93 (46.5%) patients were presented, parity show that 82 (41%) of the patients were have 4-6 parity, 86(43%) of the patients with gestational age between 28-32 weeks at examination.

In a study conduct by Mubarak AM. (16) On 80 pregnant women present with p prom. Between 24-34 wks. GA. He observed that mean age of them was 24.6-5.9 years, the parity ranged between 0-5. There was no significant difference in age, GA and parity between study groups. This study in consistent with current study.

In our study there is no statistical difference were found between G-1 and each of (gestational age p=0.49), (maternal age p=0.06), (parity p=0.2) and (gravida p=0.8) of the patients. Also, no significant difference found between Galectin-3 and gestational age (p=0.5), maternal age (p=0.2), parity (p=0.7) and gravida (p=0.9) of the patients, and this agreement with study Adewumi O *et al.* [17] and KARIMAN *et al.* [18] found that No significant statistical difference was observed between the two groups (PROM and Control) as regards age, gestational age and Parity.

The most important finding in our study, was the increase of maternal serum levels of both of galectin-1 and galectin-3 in PROM group than that in normal healthy group, the level of Galectin-1 was (11759±377) in PROM group and (11462±642) for normal group with highly significant increase in case group than that in normal group (P< 0.001). Galectin-3 was (3114±323) in PROM group and (2431±278) for normal group with highly significant increase in case group than that in normal group (P< 0.001).

which is in agreement with that mentioned by Than NG *et al.*, [19] study, which explained this difference is because these galectins are hypothetical to have controlling effects in pathways suspects in the pathophysiology of the Preterm prelabor rupture of membranes such as cellular apoptosis, cell–cell and cell–extracellular matrix interactions and immune response.

Moreover, it is in agreement with Srinivas SK *et al.*, [20] study, revealed that maternal serum galectin-1 and galectin-3 levels were increased significantly in gestations Preterm prelabor rupture of membranes in comparison with the control group.

Then NG *et al.*, [21] and Von Wolff M *et al.*, [22] concluded that Galectin 1 and galectin 3 mRNA and protein were detected in the chorioamniotic fibroblasts/myofibroblasts and macrophages, chorionic trophoblast, decidual stromal cells, endometrial glandular epithelium, activated immune cells and endothelium in addition to the amnion epithelium. They observed increased maternal serum galectin-1 and galectin-3 levels in this study support the existence of premature tissue remodeling and subsequent membrane weakening implicated in the pathogenesis of PPROM. It has been shown that galectins are multifunctional proteins that play a role in the regulation of cellular response to the oxidative stress, and galectin-1 and galectin-3 levels are up-regulated in response to oxidative stress markers; they also have regulatory roles in cellular senescence [23, 24].

Finally, we generated Receiver-Operator Characteristic (ROC) curves in order to assess the ability of Gal-1 and Gal-3 serum levels to discriminate between PROM patients and healthy controls. Both Gal-1 and Gal-3 serum levels proved to be good parameters to distinguish patients with established PROM from controls, as the area under the ROC curve (AUC) for both parameters was above 0.8 (Gal-1 AUC = 0.93, Gal-3 AUC = 0.88; both p< 0.0001). Serum Gal-1 concentrations ≥11721ng/dl (sensitivity = 94.0% and specificity = 78%) and serum Gal-3 concentrations ≥2990 ng/dl (sensitivity = 89% and specificity = 74%) successfully differentiated PROM patients from controls.

Conclusion

Significant increase of Galectin-1 and 3 in Premature rupture of membrane than that in normal group (P< 0.001).

No conflicts of interest
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Ethical clearance: Was taken from the scientific committee of the Iraqi Ministry of health

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