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Original Article

Expression and Significance of Galectin-1 and Galectin-3 in the Serum and Placental Tissues of Patients with Intrahepatic Cholestasis of Pregnancy

*Li-Hua Qian [1,2], *Xiang Kong [3,4,5], Liu-Lin Zhou [2]

1. *Clinical Medical College of Yangzhou University, No. 136 Middle Jiangyang Road, Hanjiang District, Yangzhou 225000, China*
2. *Department of Obstetrics and Gynecology, Taixing People's Hospital, No. 1 Changzheng Road, Taixing City, Taizhou 225400, China*
3. *Department of Obstetrics and Gynecology, Clinical Medical College, Yangzhou University, Yangzhou, Jiangsu, China*
4. *Institute of Translational Medicine, Medical College, Yangzhou University, Yangzhou, Jiangsu, China*
5. *Jiangsu Key Laboratory of Experimental & Translational Non-coding RNA Research, Yangzhou, Jiangsu, China*

***Corresponding Author:** Email: Kongxiang123123@163.com

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease, usually occurring in the third trimester of pregnancy. Its typical clinical manifestations are itching and elevated serum total bile acid levels, which are more harmful to the fetus, and can lead to a variety of adverse pregnancy outcomes. This paper discusses the expressions of galectin -1 and 3 in the serum and placenta of ICP patients and their relationship with the effect of the incidence of ICP.

Methods: Galectin-1 and 3 in serum and placenta were detected in 22 pregnant women with ICP and 20 healthy pregnant women admitted to the obstetrics Department of Northern Jiangsu People's Hospital from May 2021 to February 2022.

Results: Serum levels of galectin-1 and galectin-3 in ICP pregnant women were significantly higher than those in controls, with significant differences ($P<0.05$). Placental galectin-1 and 3 were higher in normal pregnant women, and there were statistical differences between groups ($P<0.05$).

Conclusion: In ICP, the maternal serum and placental galectin-1 and 3 levels were significantly increased, both of which may play an important role in the development of ICP, which may be the initiation factor of ICP pathophysiology, a marker of ICP prediction, and a target of ICP prevention strategies.

Keywords: Intrahepatic cholestasis; Pregnancy; Galectin-1; Galectin-3

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a unique complication of pregnancy, which seriously affects the health of the mother and children, and can cause serious adverse effects on both the fetus and the mother. Its typical clinical manifestations are mainly unexplained pruritus in the middle and third stages of pregnancy, usually located in the

palmoplantar area, which can spread to the limbs and trunk without skin damage, and the duration and severity of the lesion vary (1). Laboratory tests indicate the abnormal elevation of serum total bile acid (TBA) level and liver serology, and this skin itching and serological abnormalities cannot be explained by other liver diseases. However, the above clinical manifestations are reversible, usually itching symptoms and biochemical abnormalities can quickly return to normal after delivery, but the above symptoms may appear again during another pregnancy (2). Complications of pregnant women with ICP mainly include short-term complications such as right upper abdominal pain, nausea, anorexia, sleep disturbance, jaundice, and malabsorption, and serious long-term complications are rare.

In fact, ICP causes harm that is more serious to the fetus than to pregnant women, causing adverse fetal outcomes, including premature birth, respiratory distress, amniotic membrane with meconium, and a 3-to 5-fold increased risk of intrauterine fetal death (3). The global incidence of ICP is about 0.1%-10%, influenced by factors such as geographical location and ethnicity (4). So far, the etiology of ICP is not clear. The pathogenesis of ICP is affected by many factors, mainly including the superposition of hormones, immunity, environment and other factors based on genetic susceptibility (5).

The galectin family is a family of proteins with unique capabilities that can serve as a special mediator to participate in the coordination of pregnancy and regulate different developmental processes. Altered expression of galectin has been associated with abnormal pregnancy and infertility, but its association with ICP has not been reported. Galectin is a class of animal lectins with an affinity for galactosides, consisting of 15 different types of proteins, each with specific functions, which are involved in many cellular processes, including immune and inflammatory responses, mainly by binding to complementary glycoconjugates expressed on the surface of neighboring isotypic cells or in the pericellular matrix. An important function of galectin is that it can function intraccells via protein-protein interactions affecting apoptosis, cell cycle and premRNA splicing, based on which altered expression and/or function are often associated with various pathologies, suggesting their potential as biomarkers.

In the past few decades, galectin has been suggested to promote reproductive processes such as blastocyst implantation, fetal maternal immune tolerance, placental development and angiogenesis, with the two most studied galectin protein family isoforms being galectin-1 and 3 (6). Several immune cells that play an important role in the establishment and maintenance of pregnancy, such as decidual NK (dNK), macrophages, regulatory T cells, and B cells, can synthesize galectin and exert their effects on these immune cells (7). Galectin is widely expressed at the fetal-maternal interface , especially galectin-1 and 3, which are candidate factors for further investigating the pathogenesis of pregnancy complications (7).

Galectin-1 and 3 are localized to the maternal-fetal interface and participate in the interaction of cellular cells and cellular extracellular matrix, because they can bind to extracellular matrix components, they are believed to be involved in the development and maintenance of the extracellular matrix (8), and because of these properties, they are thought to play an important role in implantation, placentation (9). It is well known that galectin-1 is not only a regulator of inflammation, but also a key regulator of fetal and maternal immune tolerance during pregnancy (10). Studies have shown that an important factor in the pathogenesis of ICP is the imbalance of the maternal and fetal interface of immunity (11), and that excessive proinflammatory processes may participate in the pathogenesis (12-14). Galectin-3 is detectable in all placental trophoblast cell lines, including villous cytotrophoblast cells (CTB) and extravillous trophoblast (EVT), and placental galectin-3 deregulation is associated with obstetric complications such as spontaneous or repeated abortion, and further research is needed to understand its contribution to trophoblast biology (15,16).In addition, abnormal expression of galectin-1 and 3 is associated with obstetric complications such as preterm birth, preeclampsia and

fetal growth restriction (7), but the expression of galectin-1 and 3 has not been reported in ICP. We speculated that galectin expressed in serum and placenta may play a role in the pathophysiology of ICP.

Therefore, we aimed to detect the levels of galectin-1 and 3 in serum and placenta of ICP patients, and to compare them with healthy full-term pregnant women, to analyze the influence of the imbalance of galectin-1 and 3 in serum and placenta on the occurrence and development of ICP, and to explore its significance and potential application value in the diagnosis of ICP.

Materials and Methods

Diagnostic code

ICP diagnosis was judged according to the ICP diagnosis and treatment guidelines formulated by the scientific group of the Society of Obstetrics and Gynecology of Chinese Medical Association in 2015 (17): 1. Skin itching unexplained by other causes. 2. Fasting blood total bile acid level increased (≥10 μmol/L). 3. Bile acid level: Although bile acid level is normal, but other causes of unexplained abnormal liver function, mainly serum AST, ALT mild and moderate increase. 4. Skin itching and abnormal liver function return to normal after delivery.

The patients underwent an abdominal ultrasound to exclude abnormalities in the liver and biliary tract. Multiple pregnancy, allergic diseases, viral or nonviral hepatitis, skin diseases, tracheitis, chronic liver diseases, diseases that may cause biliary obstruction (cholelithiasis), hypothyroidism, hyperthyroidism, hypertensive diseases that may affect liver function (preeclampsia, eclampsia, and HELLP), chronic heart, kidney or lung diseases, and/or acute fatty liver disease in pregnancy were all excluded from the study. Pregnancy age was estimated from the last menstrual period and/or first-trimester ultrasound.

Case source

Twenty-two pregnant women with ICP who received regular antenatal check-up in the obstetrics clinic of Northern Jiangsu People's Hospital from May 2021 to February 2022 were selected as the experimental group and 20 healthy pregnant women as the control group.

This study was approved by the Medical Ethics Committee of our hospital. All pregnant women who participated in this study gave informed consent and signed informed consent with their families.

Data acquisition

These women were followed up until delivery. Maternal age, gestational time, delivery time, BMI, white count, total bile acid, Galectin-1, 3 levels at blood collection, gestational age at delivery, neonatal birth weight, and Galectin-1, 3 levels in placenta were recorded.

Enzyme-linked immunosorbent assay (ELISA)

Subjects: 5 ml of cubital venous blood was collected in sterile tubes before fasting administration, kept at room temperature for 30 min, centrifuged at 3,000 r/min for 15 min at 2-8 ℃, and the supernatant was removed to a new sterile EP tube at-80℃ for later analysis. The concentrations of galectin-1 and 3 in serum were detected using Galectin-1 and 3 ELISA kit (HB2513-Hu, HB1919-Hu, Shanghai Hengyuan Biotechnology LTD.), and the results were expressed in pg / mL.

Immunohistochemistry (IHC)

Placenta tissues containing decidua basalis (1 cm*1 cm *1 cm) from the surface of the placental bed were excised using forceps and scalpel, obtained from normal or ICP patients following cesarean delivery avoiding the districts of necrosis and calcification. All tissues were fixed for 24 h in 10% buffered formalin, dehydrated, and embedded in paraffin. Paraffin-embedded specimens were immunolabeled for galectin-1 and 3 following the following procedure. Paraffin-embedded tissue sections were dewaxed in xylene and rehydrated in graded ethanol, and the endogenous peroxidase activity was incubated in 1% H2O2 and 70% ethanol for 30 min. Antigen ex-

posure was performed by incubating 0.1% trypsin and 0.1% CaCl2 in PBS at 37 ℃ for 15 min, and nonspecific binding of antibodies by blocking by incubating 1% casein in PBS at room temperature. Sections were incubated with the primary antibody overnight at 4 ℃ s, followed by 30 min with the biotin secondary antibody and 30 min with the avidin-biotin peroxidase complex (ABC). Between the steps, the sections were washed three times in PBS. Reactions were observed with DAB as a chromogen. The galectin-1 antibody was purchased from Genetex, and the galectin-3 antibody was purchased from Origene, USA. Slides were then dehydrated, cleared, mounted, examined, and photographed with a Nikon E100 microscope and a Japan Nikon Nikon DS-U3 imaging system.

Immunoreactivity was looked at for staining under a light microscope by two researchers blinded to this experiment. Comprehensive score was performed with both the staining intensity and the proportion of positive cells. Semi-quantitative analysis estimated sample staining intensity: 0 indicates no response, 1 indicates the presence of both negative and trace-positive cells, 2 indicates medium, and 3 indicates strong staining. The proportion of positive cells is less than 5%, 0 points; positive cells 5% ~ 30%, 1 point; positive cells 31% ~ 60%, 2 points; positive cells more than 60%, 3 points. The two scores were the final score, 0 was negative (-), 1 to 2 weak positive (+), 3 to 4 positive (+ +), and 6 to 9 strong positive (+ + +).

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA), using W to test the distribution of all continuous variables. Comparisons between groups of variables with a normal distribution were performed by an independent sample t-test, expressed by the mean±standard deviation. Non-normally distributed variables were analyzed using the Mann Whitney u test, and the results were presented as the median and interquartile difference. Galectin-1,3 expression intensity was compared using a rank-sum test. The difference was statistically significant as P <0.05.

Results

General situations

The results of the clinical data analysis in each group are shown in Table 1. There was no significant difference between maternal age, pregnancy, parity, body mass index at blood collection, white blood cell count, and neonatal body reorganization. The gestational age at delivery of ICP group and control group was 37.9 ± 1.47 weeks and 39.68 ± 0.87 weeks, respectively, as compared between control group and ICP group (P<0.05). The TBA of ICP group and control group were: 21.55(24.1)umol/L,2.845±1.58umol/L, between TBA and ICP group (P <0.05).

Galectin-1,3 expression in peripheral blood

As shown in Table 1, serum galectin-1 serum levels in ICP patients and normal pregnant women were 55.54 ± 2.07 pg/ml and 43.59 ± 2.13pg/ml, respectively. Serum galectin-3 levels in the serum of women with ICP and normal pregnancies were 102.41 ± 3.19 and 84.51 ± 2.63, respectively. The galectin-1 and 3 levels were significantly higher in the combined ICP patients than in the controls, with the difference being statistically significant (P <0.05).

Galectin-1,3 expression in the placenta

Galectin-1 was expressed in both nucleus and cytoplasm of placental tissue, as shown in Fig. 1 (a-c). The expression level of galectin-1 in placenta of ICP group was significantly higher than that of control group, with statistical significance (P = 0.035<0.05), as shown in Table 2. Galectin-3 was mainly expressed in the trophoblastic cells of ICP patients and normal pregnant women, as shown in Fig. 1 (e-g). The expression level of Galectin-3 in placenta of ICP group was significantly higher than that of control group (P =0.018<0.05), as shown in Table 3.

Table 1: The general information in each group

Variable	*ICP(n=22)*	*Control (n=20)*	P *values*
Age (yr)	27.95±2.19	27.1±3.89	0.394
Gravidity*	1 (1)	1 (1)	0.932
Parity*	0 (1)	0 (0.75)	0.947
BMI at blood sampling (kg/m2)	25.72±3.30	26.29±2.21	0.514
GA at delivery (weeks)	37.9±1.47	39.68±0.87	< 0.001
Birth weight (kg)	3.17±0.64	3.42±0.33	0.123
TBA	21.55 (24.1)	2.85±1.58	< 0.001
WBC count	9.03±2.27	9.12±2.69	0.91
Galectin-1 (pg/ml)	55.54±2.07	43.59±2.13	< 0.001
Galectin-3 (pg/ml)	102.40±3.19	84.51±2.63	< 0.001

ICP: Intrahepatic cholestasis of pregnancy; BMI: body mass index; GA: gestational age; WBC: white blood cell.
Bold *P* values refer to statistically significant results.
* Data are presented as medians (interquartile range) and Mann-Whitney U test was used for non-normally distributed variables

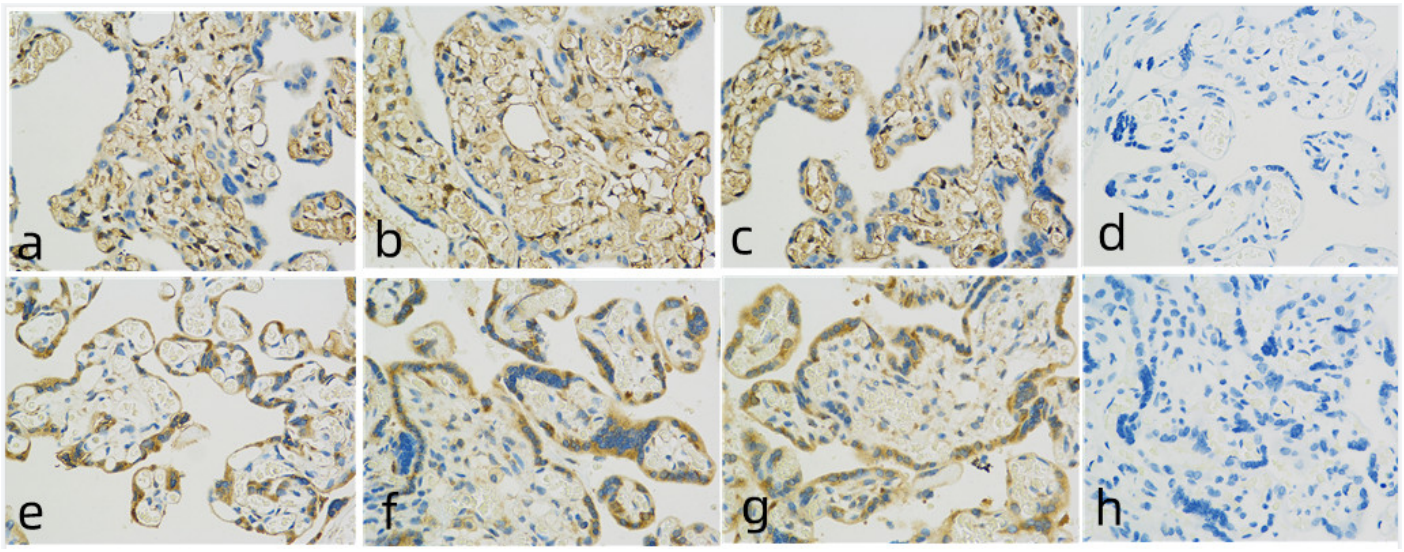

Fig. 1: Galectin-1 and galectin-3 expressions in placenta: (a) galectin-1 expressed in control group; (b、c) galectin-1 expressed in ICP group; (d) PBS as negative control; (e) galectin-3 expressed in control group; (f、g) galectin3 expressed in ICP group; (h) PBS as negative control

Table 2: Galectin-1 expression in the placenta of control group and ICP

Group	*n*	*Galectin-1 express in placenta*				P *values*
		-	+	++	+++	
ICP group	22	4	3	5	10	0.035
Control group	20	3	9	7	1	

Table 3: Galectin-3 expression in the placenta of control group and ICP

Group	*N*	*Galectin-3 express in placenta*				*P values*
		-	+	++	+++	
Icp group	22	5	2	3	2	0.018
Control group	20	5	10	3	2	

Discussion

This study aimed to test the levels of galectin-1 and 3 in pregnant women in serum and placenta of ICP, and we hypothesized that they would increase in ICP, as these galectins are thought to play a role in ICP pathophysiological pathways such as immunomodulation, immune response (18).To our knowledge, there are currently no studies of galectin-1 and 3 expressions in ICP, and our study provides the first information on the serum and placental galectin-1 and 3 levels in pregnant women with ICP. We observed higher galectin-1 and 3 levels in the serum and placenta of pregnant women with ICP compared to controls. It is concluded that galectin-1 and 3 as immunomodulators may participate in the immune response of ICP.

Galectin-1, one of the first identified galectin family members, has potent immunomodulatory functions of inhibiting neutrophil exudate, down-regulating proinflammatory factor expression, and inhibiting T cell activation, thereby reducing host immune response to allogeneic agents and enhancing immune tolerance (19,20).In activated macrophages, galectin-1 expression is up-regulated in activated macrophages, which is thought to regulate macrophage effector function in an autocrine manner during the development of an immune response (21). Galectin-1 regulates the balance of Th1 / Th2 cells by inhibiting T cell activation and inducing its apoptosis, thus regulating the balance of the immune system (22). The expression of galectin-1 in the maternal peripheral blood of preeclampsia was significantly increased (23). We note the anti-inflammatory effect of galectin-1, and this study showed substantial galectin-1 staining in the placenta of ICP patients, similar to its overexpression in the placenta of patients with severe preeclampsia, whose increased expression is thought to act as a local fetal response to exaggerated maternal systemic inflammation (24). Moreover, galectin-1-null mutant mice have a higher rate of fetal loss than wild-type mice, and recombinant galectin-1 treatment through multiple effects such as promoting the generation of tolerant dendritic cells, preventing fetal loss and re-establishing maternal-fetal tolerance (25). Based on the extensive functional data of galectin-1, we believe that galectin-1 is involved in the regulation of inflammation and the establishment of maternal and fetal immunity tolerance, and in our study, galectin-1 was significantly increased in the serum and placenta of ICP patients, which may be related to the imbalance of maternal and fetal immunity.

Increasing evidence suggests that galactose may act as both pro-inflammatory and anti-inflammatory mediators, with galectin-1 acting anti-inflammatory by blocking leukocyte infiltration and migration, while galectin-3 has pro-inflammatory effects, enhancing macrophage survival and recruitment (26). During inflammation, galactin-3 is released into the extracellular space to activate inflammatory cells, and galactin-3 may regulate inflammatory responses through its functions, including activation of immune cells, cell migration, and regulation of apoptosis (27). Exogenous galectin-3 induces mast cell degranulation (28), production of IL1 and superoxide in monocytes (29), and generation of superoxide and IL8 in neutrophils (30,31), and regulates the apoptotic neutrophils (32). Furthermore, there is evidence that galectin-3 is involved in the activation of various cell types, especially those involved in the immune response. Galectin-3 was shown to be chemotactic in both monocytes and macrophages (27). Galectin-3, a pro-

inflammatory molecule that modulates the immune response to infection and inflammation, has been previously described in villous cytotrophoblast and extravillous trophoblast, and has been shown to be involved in several biological processes (33). Overexpression of galectin-3 in human leukemic T cells is resistant to anti-fas antibodies and staurosporine-induced apoptosis (34). Cells lacking intracellular galectin-3 appear to be more prone to apoptosis, as indicated by the increased apoptosis of peritoneal macrophages in galectin-3-null mice (35). Therefore, we propose that intracellular galectin-3, as an anti-apoptotic molecule, may contribute to the survival of inflammatory cells. In this study, the galectin-1,3 levels were significantly higher in the ICP patients than in the normal pregnancy patients, which may be related to severe inflammation.

The elevated levels of maternal serum and placental galectin-1,3 observed in this study support the existence of a dysregulated state of immune balance, all of which are implicated in the pathogenesis of ICP. We observed higher serum and placental galectin-1 and 3 levels in ICP mothers than in normal pregnant women; however, the gestational age of pregnant women in the ICP group was lower than that in the normal group. It indicates that maternal serum galectin levels can be used as a prognostic factor in ICP pregnancy. Abnormal expression of galectin-1 and 3 at the maternal-fetal interface has also been associated with other obstetric syndromes such as preeclampsia, fetal growth restriction (FGR), and preterm birth (24,36,37). A growing body of data suggests that galectin can serve as a diagnostic, predictive, and prognostic biomarker of these pregnancy complications.

However, this study has some limitations; it is mainly a cross-sectional design that contains a small number of participants, and this study lacks continuous blood sampling to monitor maternal serum lectin levels from admission to delivery. Therefore, the predictive and preventive effects and the predictive value of these molecules still need further longitudinal research.

Conclusion

In our study, galectin-1 and 3 expressions were increased in serum and placenta of ICP patients compared with normal pregnancy. This result was consistent with previous studies on the relationship between other pregnancy complications and galectin-1 and 3, again providing new evidence for the involvement of galectin-1 and 3 in the regulation of pregnancy immunity. This will help further elucidate the pathogenesis of ICP.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interests.

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