

Association of Novel Hepatokine Fetuin B and Adverse Pregnancy Outcomes in Obstetric Cholestasis

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Introduction:

The Farnesoid X receptor (FXR) is a key player in the maintenance of bile acid homeostasis.

The human fetuin-B gene is a FXR agonist-regulated gene.

Raised serum fetuin B levels in cases of IHCP can be used as a biomarker.

Objectives:

Primary objective:

To evaluate the relationship between serum fetuin B and IHCP in Indian population.

Secondary objective:

To investigate the association between serum fetuin B and adverse pregnancy outcomes.

To study the incidence of IHCP in eastern India.

Method:

Type of study: Prospective comparative study.

Ethics: IEC approval and patient consent obtained.

Inclusion: 60 singleton pregnant women with IHCP and 60 healthy matched pregnant women in the third trimester.

Exclusion: Pregnant women with alternative causes of hepatic dysfunctions ,metabolic, thyroid, skin, hypertension disorders

All the patients were followed prospectively till delivery and data between the two groups were compared.

Result: The incidence of IHCP in our study is 2.3%.

Table 1: The Demographic and Laboratory parameters of the IHCP and control groups				Table 2: Comparisons of obstetric, perinatal and neonatal outcomes outcome between both the groups			
Parameters	Group		p value	Parameters	Group		p value
	IHCP Cases (n = 60)	Non IHCP Controls (n = 60)			IHCP Cases (n = 60)	Non- IHCP Controls (n = 60)	
Age (Years)	27.63 ± 4.37	26.73 ± 4.82	0.164 ¹	POG at Delivery (Weeks)***	37.18 ± 1.52	38.07 ± 1.51	0.001 ¹
BMI (Kg/m²)	24.30 ± 4.13	24.71 ± 3.88	0.385 ¹	Induced Labour (Yes)***	37 (61.7%)	25 (41.0%)	0.023 ³
Gravida			0.577 ³	Spontaneous Labour (Yes)***	22 (36.7%)	9 (15.0%)	0.007 ³
Primigravida	34 (56.7%)	37 (61.7%)		LSCS (Yes)***	53 (88.3%)	42 (70.0%)	0.013 ³
Multigravida	26 (43.3%)	23 (38.3%)		Vaginal Delivery (Yes)***	7 (11.7%)	18 (30.0%)	0.013 ³
POG at blood sampling (Weeks)	35.42 ± 2.35	35.08 ± 2.37	0.510 ¹	Elective CS (Yes)	18 (30.0%)	21 (35.0%)	0.699 ³
Past H/O IHCP (Yes)***	8 (13.3%)	1 (1.7%)	0.032 ⁴	Emergency CS (Yes)***	35 (58.3%)	21 (35.0%)	0.010 ³
S. Bile Acids (µmol/L)***	26.58 ± 17.54	4.13 ± 2.79	<0.001 ¹	Preterm Delivery (Yes)	13 (21.7%)	6 (10.0%)	0.080 ³
ALT (IU/L)***	139.52 ± 85.10	26.18 ± 23.32	<0.001 ¹	Iatrogenic Preterm (Yes)***	10 (16.7%)	3 (5.0%)	0.040 ³
AST (IU/L)***	113.88 ± 75.66	22.92 ± 13.86	<0.001 ¹	Spontaneous Preterm (Yes)	3 (5.0%)	3 (5.0%)	1.000 ⁴
Total Bilirubin (mg/dL)***	0.72 ± 0.38	0.48 ± 0.19	<0.001 ¹	Term Delivery (Yes)	47 (78.3%)	54 (90.0%)	0.080 ³
GGT (IU/L)***	32.23 ± 18.37	12.38 ± 16.20	<0.001 ¹	Birth Weight (g)	2735.32 ± 593.93	2846.73 ± 494.20	0.266 ²
S. Fetuin-B (pg/mL)	77893.85 ± 74855.74	55608.84 ± 38492.48	0.105 ¹	Birth Weight ≤ 2500 g (Yes)	19 (31.7%)	18 (30.0%)	0.843 ³
***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: t-test, 3: Chi-Squared Test, 4: Fisher's Exact Test, (POG- Period of gestation, IU/dL- Intrauterine fetal demise)				Birth Weight ≤10th Percentile (Yes)	18 (30.0%)	21 (35.0%)	0.559 ³
				NICU Admission (Yes)***	13 (21.6%)	3 (5.0%)	0.007 ³
				MSL (Yes)***	23 (38.3%)	13 (21.7%)	0.048 ³
				Stillbirth (Yes)	0 (0.0%)	0 (0.0%)	1.000 ³
				Pathological CTG (Yes)***	25 (41.7%)	7 (11.7%)	<0.001 ³
				Composite adverse Maternal Outcome (Yes)	8 (13.3%)	6 (10.0%)	0.570 ³
				Composite adverse Neonatal Outcome (Yes)	14 (23.3%)	6 (10.0%)	0.051 ³
				***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: t-test, 3: Chi-Squared Test, 4: Fisher's Exact Test, (POG-Period of gestation, LSCA- Lower segment Caesarean section, NICU- Neonatal intensive care unit, MSL -Meconium-stained liquor, CTG- Cardiotocograph)			

Table:3a, Correlation analysis of TBAs and Serum Fetuin B in IHCP / Case group								
	Age (years)	BMI (kg/m²)	GA at Sampling (weeks)	AST (IU/L)	ALT (IU/L)	GGT (IU/L)	TBAs (µmol/L)	Serum total Bilirubin (mg/dl)
IHCP group (n = 60), r	0.08	-0.25	0.51	0.56	0.58	0.077	-	0.51
S. TBAs (µmol/L) P	0.50	0.54	0.00003*	<0.00001*	< 0.00001*	0. 595	-	<0.00003*
IHCP group (n=60) r	0.039	-0.022	0.131	0.037	0.164	-0.082	0.288	0.039
S. Fetuin B (pg/ml) p	0.797	0.867	0.153	0.773	0.210	0.503	0.025*	0.767
* Correlation is significant at the 0.05 level (2-tailed).								
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; TBAs: total bile acids; GA: gestational age; IHCP: intrahepatic cholestasis of pregnancy.								
Bold p values refer to statistically significant results								

Table:3b, Correlation analysis of TBAs and Serum Fetuin B in IHCP / Case group							
	GA at Delivery (weeks)	Birth weight (gms)	NICU Admission	MSL	Pathological CTG	Composite Adverse Neonatal Outcomes	Composite Adverse Maternal Outcomes
IHCP group (n = 60), r	0.148 (p- 0.259)	-0.29(p-0.04)					
Sub TBAs (µmol/L)			0.22	0.38	0.27	0.23	0.27
IHCP group (n=60) r	0.049 (p- 0.761)	0.15 (p-0.24)					
Sub S. Fetuin B (pg/ml)			0.02	0.14	0.13	0.06	0.01
* Spearman Correlation is significant at the 0.05 level (2-tailed). Bold p values refer to statistically significant results Strength of Association (Sub Point-Biserial Correlation)							
TBAs: total bile acids; GA: gestational age; IHCP: intrahepatic cholestasis of pregnancy, NICU- Neonatal intensive care unit, MSL -Meconium-stained liquor, CTG- Cardiotocograph).							

Table 4: Comparison of the Diagnostic Performance of Various Predictors in Predicting Group: Case vs Group: Control (120)

Predictor	AUROC	95% CI	P	Sn	Sp	PPV	NPV	DA
S. Fetuin-B (pg/ml)	0.586	0.483-0.689	0.105	68%	53%	59%	63%	61%
S. Bile Acids (µmol/L)	0.998	0.996-1	<0.001	100%	95%	95%	100%	98%

AUROC: Area under ROC curve; CI: Confidence interval; P: P value; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; DA: Diagnostic Accuracy.

Discussion Cont...The correlation analysis didn’t reveal a correlation between S. fetuin B and biochemical parameters, obstetrics, perinatal outcomes except with serum TBAs. This could be due to small sampling size and lack of serial testing at different time points during pregnancy.

Discussion: This study showed that serum fetuin B concentrations did not vary significantly between pregnancies complicated by IHCP and healthy pregnancies.

Conclusion: Thus, serum Fetuin B was not shown to be an effective marker for use in IHCP.