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Original Research Article

Correlation of maternal serum bile acid induced placental inflammation by Gpbar-1 and NF-κB pathway with fetal outcome in intrahepatic cholestasis of pregnancy: a case control study

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (IHCP) is a pregnancy-specific liver disorder associated with adverse fetal outcomes. Elevated maternal serum bile acids (BAs) trigger placental inflammation through the G-protein-coupled bile acid receptor 1 (Gpbar-1) and nuclear factor Kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. This study investigates Gpbar-1 and NF-κB gene expression in placental tissue of IHCP patients and its correlation with fetal outcomes.
Methods: This prospective case-control study, conducted between November 2019 and October 2021 at a tertiary care hospital, included 30 diagnosed IHCP cases and 30 gestational age-matched healthy controls. Serum bile acid levels were measured (using Elisa), and placental tissue was analyzed post-delivery using quantitative reverse transcription PCR (RT-qPCR) for Gpbar-1 and NF-κB gene expression. Maternal and fetal outcomes such as preterm delivery, fetal distress, low APGAR score, meconium-stained liquor, and NICU admission were recorded.
Results: Serum bile acid levels were significantly higher in IHCP cases ($p<0.001$). Gene expression analysis showed a 2.192-fold upregulation of Gpbar-1 ($p=0.019$) and a 2.396 -fold upregulation of NF-κB in IHCP placentas ($p=0.029$). Adverse fetal outcomes were not significantly correlated with higher gene expression.
Conclusions: Elevated bile acid levels in IHCP activate the Gpbar-1/NF-κB pathway, leading to placental inflammation and adverse fetal outcomes. Targeting this pathway may improve pregnancy outcomes in IHCP. Further research on anti-inflammatory therapies is recommended.

Keywords: Intrahepatic cholestasis of pregnancy, Bile acids, Placental inflammation, Gpbar-1, NF-κB, Ursodeoxycholic acid, Gene expression, Fetal outcome, Maternal and neonatal complications

INTRODUCTION

The worldwide prevalence of IHCP ranges from 0.3% to 5.6% with an incidence of 2% to 8.2% in India.[1-3] IHCP has a complex, multifactorial etiology involving genetic, hormonal, environmental, and dietary factors.[4,5] Disruption of fetal-maternal homeostasis leads to impaired bile excretion, triggering upregulation of canalicular transporters, a process enhanced by ursodeoxycholic acid (UDCA).

Elevated BAs act as proinflammatory ligands, causing placental inflammation through the Gpbar-1 and NF-κB pathway.[6-9] Gpbar-1, a membrane-bound receptor, internalizes upon BA binding, influencing inflammatory gene expression.[7,8] NF-κB, in its inactive form, resides in the cytosol with IκBα.[10,11] Activation of Gpbar-1 in

trophoblasts triggers NF-κB; IκBα undergo proteasome degradation and nuclear translocation of p65 subunit of NF-κB, p65 subunit binds to its response element on DNA and upregulate the VCAM-1, IL-4 and TNF-α gene expression.[6,10,11] They act as inflammatory mediators, leading to leukocyte recruitment to placental tissue and produces placental damage which affects its functions.[12-14] UDCA competitively inhibits BAs at Gpbar-1, reducing inflammation, while Andrographolide, a direct NF-κB blocker, is considered more effective. Anti-inflammatory therapies targeting this pathway may improve IHCP management (Figure 1).[6]

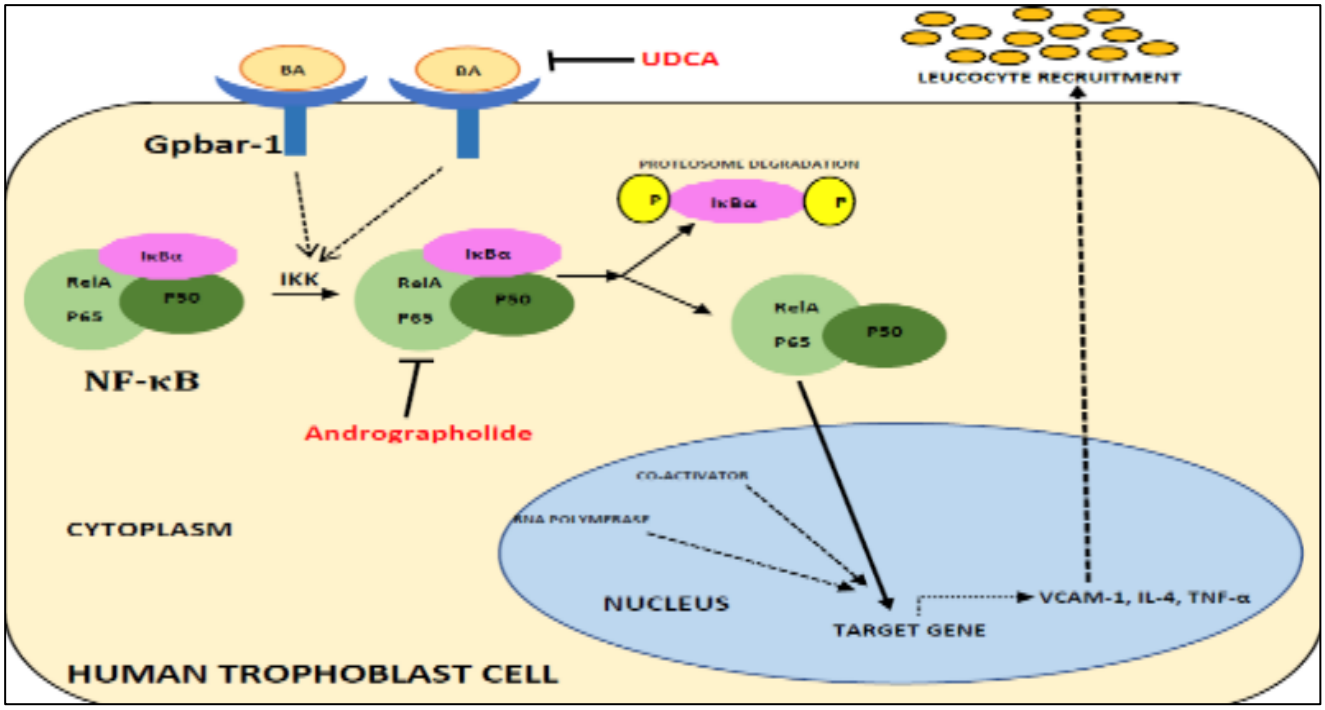

Figure 1: Bile acid induced placental inflammation through Gpbar-1 and NF-kB.

*(Adapted from Zhang et al).[6] Schematic representation of bile acid–induced placental inflammation mediated through the Gpbar-1/NF-κB signaling pathway in placental trophoblast cells. Binding of BA to Gpbar-1activates the IKK complex, resulting in phosphorylation and proteasomal degradation of IκBα, which releases the NF-κB (p65/p50) transcription complex. Activated NF-κB translocates to the nucleus and induces transcription of inflammatory mediators including VCAM-1, IL-4, and TNF-α, promoting leukocyte recruitment and placental inflammation. UDCA inhibits bile acid interaction with Gpbar-1, while andrographolide suppresses NF-κB activation.

Increased serum bile acid levels, which serve as a key diagnostic marker, was linked to higher fetal complications.[15-17] Early detection and treatment are crucial in improving pregnancy outcomes.[17,18] The aim of this study is to understand the placental molecular level changes in form of Gpbar-1 and NF-κB gene expression and induced maternal and fetal complications. Current study might be proved as a milestone in upcoming treatment strategies of IHCP.

METHODS

This study aimed to investigate maternal serum bile acid-induced placental inflammation via Gpbar-1 and NF-κB pathways and its correlation with fetal outcomes in IHCP. The primary objective was to measure the expression of Gpbar-1 and NF-κB in the placenta and correlate these with fetal outcomes in IHCP patients. Secondary objectives included comparing fetal outcomes between mild and severe IHCP cases and controls, observing obstetric outcomes in IHCP. It is conducted as a case-control study in collaboration between the departments of Obstetrics and Gynaecology, Paediatrics and Biochemistry from November 2019 to October 2021 at a tertiary hospital. The study included singleton pregnancies in the third trimester (>28 weeks), maternal age between 18-34 years, spontaneous conception, and diagnosed IHCP cases n=30 and controls n=30 were taken. Exclusion criteria were multiple pregnancies, pregnancies with anomalous fetuses, other obstetric complications, chronic illnesses, collagen vascular diseases, and substance abuse. Healthy pregnant women matched for age and gestational age were recruited as controls.

Venous blood samples (2 ml) were collected after overnight fasting from all participants at enrolment, with serum bile acid measured using a commercial human total bile acid (TBA) ELISA kit (Bioassay technology laboratory, Shanghai, China; Cat. No. E1422Hu) using sandwich ELISA principle, with the optical density (OD) measured at 450 nm. Cases were followed until 37 weeks and induced for labor, while controls were followed until

delivery. Obstetric and fetal outcomes were recorded for both groups. At delivery, placental tissue was collected for gene expression analysis of Gpbar-1 and NF-κB using quantitative RT-qPCR.

RT qPCR was performed to measure the expression of Gpbar-1 and NF-KB genes on CFX Connect™ Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA) using primer sequences (Table 1). In this study, expression normalization was done by GAPDH gene. Relative gene expression of Gpbar-1 and NF-κB was calculated using the 2^−ΔΔCt method, with GAPDH as the internal housekeeping gene.

All cases were followed until 37 weeks, after which pregnancy was terminated by elective induction of labor.

In the control group, delivery occurred either by induction or spontaneous labor. Obstetric complications, such as preterm labor, PIH, GDM, abruption, MSL, PTPROM, fetal distress, or IUD, were managed according to standard protocols. Fetal and neonatal outcomes, including prematurity, fetal distress, IUD, stillbirth, MAS, birth weight, APGAR score, and NICU admission, were recorded. At delivery, placental tissue was collected from both groups for gene expression analysis (Gpbar-1, NF-κB). A 2×2×2 cm placental tissue sample was obtained and were washed in ice-cold phosphate-buffered saline (PBS) to remove maternal blood, immediately flash-frozen and then stored at -80°C for subsequent molecular analysis.

This protocol ensured the maintenance of RNA integrity by minimizing the activity of endogenous RNases before storage (Figure 2).

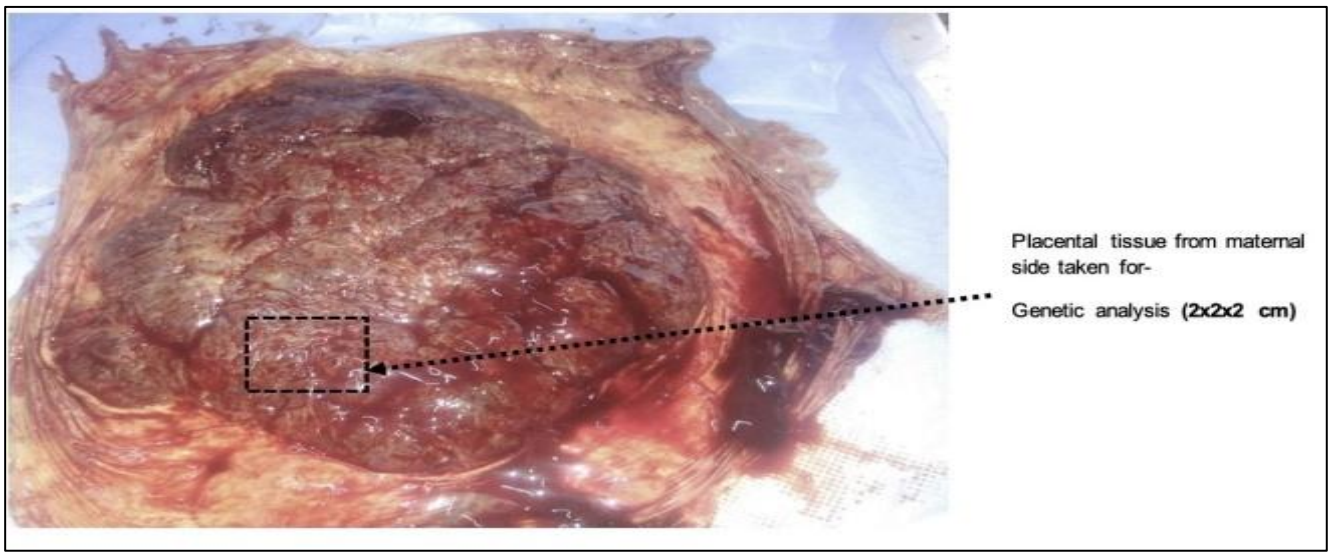

Figure 2: Placental tissue for genetic analysis.

*Placental tissue sampling for molecular analysis. A 2×2×2 cm biopsy specimen was obtained from the maternal surface of the placenta immediately after delivery for gene expression analysis. The highlighted area indicates the sampling site used for RNA extraction and subsequent RT-qPCR analysis of Gpbar-1 and NF-κB gene expression.

Ethical clearance was obtained from institutional ethical clearance committee for human research. An informed written consent was taken from all the participants after enrolment.

RESULTS

A total of 60 pregnant women in the third trimester were included in the study, comprising 30 cases of IHCP and 30 healthy controls. Among the IHCP cases, 22 (73.3%) were classified as mild IHCP and 8 (26.7%) as severe IHCP based on serum bile acid levels.

Serum TBA levels were significantly higher in severe IHCP compared with mild IHCP. The mean TBA level in mild IHCP was 15.72±2.38 µmol/L with a range of 10.037-18.43 µmol/L, whereas in severe IHCP the mean level was 64.14±15.95 µmol/L with a range of 47.465–95.415 µmol/L. This difference was statistically highly significant ($p<0.001$), indicating a marked increase in bile acid levels with increasing disease severity (Table 2).

Adverse maternal outcomes were observed in 19 (63.33%) IHCP cases compared with 8 (26.67%) controls ($p=0.015$). The most common complication was meconium-stained liquor (36.67% vs 10%), followed by preterm labour (23.33% vs 6.67%). Induction of labour was performed in 56.67% cases and 36.67% controls, while caesarean section occurred in 30% cases compared with 10% controls, though these differences were not statistically significant. Fetal complications occurred in 17 (56.67%) cases and 6 (20%) controls ($p=0.005$), with prematurity (26.67%) and small-for-gestational-age infants (20%) being the most frequent. Mean birth weight was significantly lower in IHCP cases (2.59±0.52 kg) than

controls (2.96±0.29 kg; p=0.001). NICU admission was required in 63.33% of IHCP neonates compared with 20% of controls (p=0.001) (Table 3). Placental inflammatory gene analysis demonstrated 2.192-fold upregulation of Gpbar-1 (p=0.019) and 2.396-fold upregulation of NF-κB (p=0.029) in IHCP cases compared with controls. These findings indicate a possible association between BA-induced placental inflammation and adverse pregnancy outcomes in IHCP (Table 4).

Spearman's rho analysis demonstrated no significant correlation between placental Gpbar-1 or NF-κB gene expression and fetal outcomes in either group. In cases, weak correlations were observed with fetal outcome, APGAR scores, NICU admission, and neonatal death (p>0.05). Similarly, controls showed very weak and statistically non-significant correlations between inflammatory gene expression and neonatal parameters (Table 5).

Table 1: Primer sequences.

Genes	Forward	Reverse
Gpbar-1	F5'GAGACGTGCACTTGGTCGTG-3'	R5'-TCCATCTACAAGGCAGCACC-3'
NF-κB	F5'-GAGACGTCTGCATGGTCGTG-3'	R5'-TCCATATCCAAGGCAGCACC-3'
GAPDH	F5' CCA AGG TCA TCC ATG ACA ACT TTG GT 3'	R5' TGT TGA AGT CAG AGG AGA CCA CCT G 3'

Table 2: Comparison of serum TBA levels in mild and severe category of IHCP cases.

Variables	Mild IHCP, (n=22)	Severe IHCP, (n=8)	P value
Range	10.037-18.43	47.465-95.415	<0.001*
Mean SD	15.72±2.38	64.14±15.95	<0.001*

*p<0.05 is significant; Independent T test

Table 3: Comparison of feto-maternal outcome in cases and controls.

Parameters of obstetric outcome	Cases, (n=30)	Controls, n=30)	P value
Maternal complications			
No complications	11 (36.67%)	22 (73.33%)	0.015*[1]
Preterm labour (PTL)	7 (23.33%)	2 (6.67%)	
Preterm premature rupture of membrane (PTPROM)	1 (3.33%)	1 (3.33%)	
Abruption	1 (3.33%)	0 (0%)	
Meconium-stained liquor (MSL)	11 (36.67%)	3 (10%)	
Post-partum haemorrhage (PPH)	2 (6.67%)	2 (6.67%)	
Labour			
Induction	17 (56.67%)	11 (36.67%)	0.302[2]
Mode of delivery			
Vaginal	20 (66.67%)	26 (86.67%)	0.104[2]
Instrumental (forceps)	1 (3.33%)	1 (3.33%)	
Caesarean	9 (30%)	3 (10%)	

*p<0.05 is significant; 1- Fisher's exact test; 2- Chi square test

Table 4: Comparison of maternal outcome with Gpbar-1 and NF-κB gene expression in cases and controls.

Parameters of fetal outcome	Cases, (n=30)	Controls, (n=30)	P value
Fetal complications			
No complications	13 (43.33%)	24 (80%)	0.005*[1]
Fetal distress	3 (10%)	1 (3.33%)	
Prematurity	8 (26.67%)	3 (10%)	
Meconium aspiration syndrome (MAS)	2 (6.67%)	0 (0%)	
Small for gestational age (SGA)	6 (20%)	2 (6.67%)	
APGAR score			
APGAR score at 1 minute (Mean±SD)	8.86±1.066	9.20±0.805	0.069*[4]
APGAR score at 5 minutes (Mean±SD)	9.23±0.898	9.60±0.498	0.147*[4]
Birth weight (Mean±SD) (Kg)	2.59±0.52	2.96±0.29	0.001*[3]
NICU admission	19 (63.33%)	6 (20%)	0.001*[2]
Baby expired after birth	2 (6.67%)	0 (0%)	0.492*[1]

*p<0.05 is significant; 1- Fisher's exact test; 2- Chi square test; 3- Independent T-test; 4- Mann-Whitney test

Table 4: Comparison of maternal outcome with Gpbar-1 and NF-κB gene expression in cases and controls.

Gene expression	Cases, (n=19) Mean of d Ct	Controls, (n=8) Mean of d Ct	Fold change of cases	P value
Gpbar-1 gene	2.876±1.098	1.744±0.974	2.192 upregulation	0.019*
NF-κB gene	2.572±1.516	1.312±0.632	2.396 upregulation	0.029*

*p<0.05 is significant

Table 5: Correlation of fetal outcome with Gpbar-1 and NF-κB gene expression in cases and in controls.

Spearman's rho coefficient	Cases, (n=30)		Controls, (n=30)	
	Correlation coefficient	P value	Correlation coefficient	P value
Fetal outcome				
Gpbar-1 gene	-0.026	0.891	-0.029	0.800
NF-κB gene	-0.028	0.882	-0.041	0.991
APGAR score at 1 minute				
Gpbar-1 gene	-0.030	0.875	0.073	0.701
NF-κB gene	-0.081	0.672	0.075	0.688
APGAR score at 5 minutes				
Gpbar-1 gene	0.140	0.462	0.063	0.741
NF-κB gene	0.008	0.968	-0.019	0.921
NICU admission				
Gpbar-1 gene	0.012	0.951	0.202	0.286
NF-κB gene	0.087	0.643	0.087	0.643
Baby expired after birth				
Gpbar-1 gene	0.139	0.464	----	----
NF-κB gene	0.124	0.515	----	----

DISCUSSION

IHCP is characterized by impaired hepatobiliary transport leading to accumulation of BAs in maternal circulation and the fetoplacental unit. Elevated maternal serum BAs are considered the principal biochemical hallmark of the disease and are strongly associated with adverse obstetric and neonatal outcomes. In the present study, maternal serum TBA levels were significantly higher in IHCP cases compared with controls, with mean values of 15.72±2.38 µmol/l in mild IHCP and 64.14±15.95 µmol/l in severe IHCP compared with 7.22±1.92 µmol/l in controls (p<0.001). These findings are consistent with the observations of Brouwers et al and Glantz et al who demonstrated that increasing bile acid concentrations correlate with disease severity and a higher risk of fetal complications.[19,20] Similar elevations in bile acid levels have also been reported in studies by Pata et al, Du et and Chen et al further supporting the role of BAs as key mediators in the pathophysiology of IHCP.[16,21,22]

In addition to their role in cholestasis, BAs function as signaling molecules capable of activating inflammatory pathways. In the present study, placental expression of Gpbar-1 and NF-κB genes was significantly upregulated in IHCP cases, with 2.192-fold and 2.396-fold increases respectively compared with controls. This finding suggests that elevated BAs may trigger placental inflammation through activation of the Gpbar-1/NF-κB signaling pathway. Experimental studies have demonstrated similar mechanisms, where exposure of trophoblast cells to elevated BAs activates inflammatory mediators through this pathway.[6] Moreover, molecular analyses by Du et al have reported dysregulation of genes involved in immune and inflammatory signaling pathways in placental tissue from IHCP patients.[22] Such inflammatory activation may impair placental vascular and metabolic functions, thereby contributing to adverse pregnancy outcomes.

The clinical consequences of bile acid–induced placental inflammation were reflected in the maternal outcomes observed in the present study. Adverse maternal outcomes were observed in 63.3% of IHCP cases compared with 26.7% of controls (p=0.015). The most frequent complication was meconium-stained liquor, observed in 10 mild cases and one severe case, followed by preterm delivery in 23.3% of cases compared with 6.7% of controls. These findings are comparable with previous studies by Glantz et al, Brouwers et al, and Shemer et al which reported higher risks of preterm birth and obstetric complications among women with IHCP.[19,20,23]

Similarly, adverse fetal outcomes were significantly more frequent among IHCP cases in the present study. Fetal complications occurred in 56.7% of cases compared with 20% of controls (p=0.005), with prematurity (26.7%) and small-for-gestational-age infants (20%) being the most common outcomes. In addition, 63.33% of neonates in the IHCP group required NICU admission compared with

20% in controls (p=0.001), and mean birth weight was significantly lower in cases (2.59±0.52 kg vs 2.96±0.29 kg; p=0.001). Similar findings have been reported in several studies demonstrating increased rates of prematurity, neonatal complications, and NICU admission in pregnancies complicated by IHCP.[20,23,24]

Although placental Gpbar-1 and NF-κB expression was higher in cases with fetal complications, the correlation did not reach statistical significance. This may be attributed to the relatively small sample size, particularly the limited number of severe IHCP cases in the study, which may reduce statistical power. Additionally, fetal outcomes in IHCP are likely influenced by multiple interacting factors, including bile acid concentration, gestational age at delivery, placental function, and clinical interventions such as early induction of labour. These factors may partly explain the absence of a statistically significant correlation despite the observed trend of increased gene expression.

Overall, the present study supports the concept that elevated maternal BAs in IHCP may contribute to placental inflammation through activation of the Gpbar-1/NF-κB pathway, potentially leading to adverse maternal and fetal outcomes.

Limitations

This study has few limitations. First, the sample size was relatively small, which may limit the generalizability of the findings to the broader population. Second, the study was conducted at a single tertiary care center, which may introduce institutional bias. Third, the analysis focused only on gene expression levels of Gpbar-1 and NF-κB, and did not evaluate corresponding protein expression or downstream inflammatory cytokines, which could provide a more comprehensive understanding of the inflammatory pathway. Additionally, the cross-sectional assessment of placental tissue at delivery does not fully capture dynamic molecular changes occurring throughout pregnancy. Future multicentric studies with larger sample sizes and detailed molecular analysis including cytokine profiling are required to further validate these findings.

CONCLUSION

While Gpbar-1 and NF-κB were significantly upregulated in IHCP placentas, their expression levels did not linearly correlate with the severity of fetal outcomes, likely due to the small sample size of severe cases.

This study highlights the significant role of maternal serum bile acid-induced placental inflammation mediated by Gpbar-1 and NF-κB pathway in the pathogenesis of IHCP and its impact on fetal outcomes. While Gpbar-1 and NF-κB were significantly upregulated in IHCP placentas, their expression levels did not linearly correlate with the severity of fetal outcomes, likely due to the small sample size of severe cases. This inflammatory response was associated with increased rates of preterm birth, fetal distress, meconium-stained liquor, low APGAR scores, NICU admissions, and other adverse neonatal outcomes.

This emphasizes the importance of early diagnosis, prompt management, and targeted therapeutic approaches to reduce placental inflammation and improve fetal outcomes in IHCP cases. Future research focusing on therapeutic agents targeting the Gpbar-1 and NF-κB pathways may provide promising avenues for minimizing the adverse effects of IHCP on pregnancy outcomes.

Thus, the findings of this study could serve as a stepping stone for future investigations aimed at developing novel anti-inflammatory treatments for IHCP, ultimately improving maternal and fetal health.

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