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Serum placental growth factor, total cholesterol, and triglycerides for prediction of intrahepatic cholestasis of pregnancy

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Abstract

This study aims to investigate the predictive values of serum placental growth factor (PIGF), total cholesterol (TC), and triglycerides (TG) in the context of intrahepatic cholestasis of pregnancy (ICP). This retrospective case control study recruited pregnant women from January 2021 to December 2021 at the Maternal and Child Health Hospital of Hunan Province, encompassing pregnant women diagnosed with ICP and those with unremarkable prenatal examinations. A total of 433 pregnant women were included, among whom 167 were diagnosed with ICP after 24 weeks of pregnancy. Patients with ICP exhibited an average age of 31.30 ± 4.54 years and an average pregnancy week at delivery of 37.63 ± 1.45 weeks. Multivariable regression analysis showed that the pregnancy week at delivery (OR = 0.823, 95% CI: 0.769–0.879, $P < .001$), PIGF (OR = 0.994, 95% CI: 0.992–0.996, $P < .001$), TC (OR = 1.955, 95% CI: 1.586–2.409, $P < .001$), and TG (OR = 3.786, 95% CI: 2.655–5.399, $P < .001$) were independent risk factors for ICP. The area under the curve values for PIGF, TC, and TG in predicting ICP were 0.858 (95% CI: 0.822–0.893), 0.721 (95% CI: 0.670–0.772), and 0.830 (95% CI: 0.788–0.871), respectively. However, their combination yielded an area under the curve value of 0.922 (95% CI: 0.898–0.946). The composite assessment of PIGF, TC, and TG demonstrates potential efficacy in predicting ICP among pregnant women.

Abbreviations: AUC = area under the curve, FBG = fasting blood glucose, ICP = intrahepatic cholestasis of pregnancy, PIGF = placental growth factor, TBA = total bile acids, TC = total cholesterol, TG = triglycerides.

Keywords: case control study, intrahepatic cholestasis of pregnancy, placental growth factor, predictive value, total cholesterol, triglyceride

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a gestational complication that arises during the mid-to-late stages of pregnancy. It is characterized by symptoms like pruritus, icterus, and liver dysfunction, particularly elevated total bile acids (TBA) levels.[1–3] The incidence rate of this condition ranges from 0.3% to 5.6%, with variations based on race, familial history, geography, and seasonality.[4,5] Generally, the prognosis for pregnant women affected by ICP is favorable. Pruritus typically subsides shortly after delivery, while TBA concentrations and other liver function markers return to baseline without notable liver consequences.[6] Nonetheless, the correlation between elevated TBA levels and severe adverse perinatal outcomes, including premature delivery (19%–60%), fetal distress (22%–41%), and even stillbirth (0.4%–4.1%), warrants attention.[7,8] Prompt diagnosis and appropriate interventions are pivotal in curbing adverse pregnancy outcomes in ICP patients.

Serum TBA concentration stands as a vital diagnostic biomarker for detecting and monitoring the progression of ICP.[9] However, an elevated TBA level alone does not possess the ability to predict the onset of the condition. Remarkably, a substantial proportion of pregnant women with TBA levels equal to or exceeding 10 μmol/L may exhibit no clinical indications of ICP during their medical evaluations.[10] Consequently, the identification of potential predictors capable of diagnosing ICP before clinical symptoms manifest is of paramount importance.

The establishment and maintenance of placental function hinge upon the initiation of a low-resistance uteroplacental

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Informed consent forms were signed by all pregnant women who participated.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The research adhered to the principles of the Declaration of Helsinki. The study received approval from the Medical Ethics Committee of the Maternal and Child Health Hospital of Hunan Province (#202005).

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circulation, a phenomenon strongly intertwined with trophoblast cell infiltration and placental vasoganglion function.[11] This intricate process entails the harmonious interplay of numerous angiogenic factors, among which placental growth factor (PIGF) assumes a vital role.[12] Prior studies have demonstrated that disrupted lipid profiles can influence a woman's fertility.[13–15] Furthermore, a preceding investigation has elucidated a correlation between ICP and disrupted lipid profiles.[16] Notably, individuals afflicted by ICP exhibit markedly elevated levels of triglycerides (TC), total cholesterol (TG), and low-density lipoprotein, concomitant with a reduction in high-density lipoprotein concentration, when compared to their healthy pregnant counterparts.[17] While a number of studies have scrutinized the prognostic utility of specific biochemical markers such as aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase in the context of ICP, no investigations to date have addressed the predictive significance of PIGF, TC, and TG.[18,19]

This study aims to examine the predictive values of serum PIGF, TC, and TG for the onset of ICP.

2. Methods

2.1. Study design and patients

This retrospective case control study was conducted at the Maternal and Child Health Hospital of Hunan Province, enrolling pregnant women between January 2021 and December 2021.

Inclusion criteria were as follows: (1) Pregnant women aged between 20 and 45 years; (2) Pregnant women in the mid-to-late stages of gestation; (3) Pregnancies involving singleton live births. Exclusion criteria encompassed: (1) Severe anemia, gestational diabetes mellitus, chronic liver and kidney diseases, as well as severe conditions affecting the heart, liver, brain, kidneys, and other organs; (2) Mental illnesses and communication disorders; (3) Incomplete obstetric examination data.

Pregnant women who satisfied the diagnostic criteria for ICP in accordance with the ICP Diagnosis and Treatment Guide (2015) formulated by the Obstetrics Group of the Chinese Society of Obstetrics[20] were clinically identified with ICP. The diagnostic criteria consisted of persistent skin pruritus primarily affecting the palms and soles of the feet, not attributable to other causes (with differentiation from other pregnancy-related skin conditions necessitating consideration of severe skin itching), fasting blood TBA levels ≥10 μmol/L, normal bile acid levels coupled with unexplained liver function abnormalities (typically mild to moderate elevation in serum ALT and aspartate aminotransferase levels, possibly with increased gamma-glutamyl transferase levels, alongside heightened serum bilirubin [TBIL] levels, predominantly direct bilirubin [DBIL] levels), and pruritus typically subsiding within 1 to 2 days post-delivery, accompanied by the normalization of liver function indicators within 4 to 6 weeks following delivery.

The study received approval from the Medical Ethics Committee of the Maternal and Child Health Hospital of Hunan Province (Approval #202005). Informed consent forms were signed by all participating pregnant women.

2.2. Data collection

General data were extracted from electronic medical records, encompassing parameters such as age, pregnancy week at delivery, number of pregnancies, number of deliveries, gestational body mass index, , TC, and TG, and fasting blood glucose (FBG) levels at the 24th week of pregnancy. TBA levels were assessed at both the 12th week and later in the second and third trimesters of pregnancy. If the TBA level exceeded 10 μmol/L, it underwent further evaluation at the outpatient clinic. The values for PIGF, TC, TG, TBA, and FBG documented in the electronic medical records were derived from serum concentrations quantified using enzyme-linked immunosorbent assay (ELISA). The TBA kits, TC kits, TG kits, and FBG kits were all manufactured by Shanghai Kehua Bio-Engineering Co., Ltd., while the PIGF kit originated from Suzhou Sym-bio-Co.

2.3. Statistical analysis

The statistical analysis was executed employing SPSS Statistics version 24.0 (IBM, Armonk, NY). Continuous data with a normal distribution were expressed as means ± standard deviations and assessed using Student *t* test; otherwise, they were represented as medians (interquartile range, IQR) and subjected to analysis via the Wilcoxon rank-sum test. Categorical data were presented as n (%) and subjected to analysis using either the chi-square test or Fisher exact test. Multivariable logistic regression analysis was employed to pinpoint independent risk factors associated with ICP. The diagnostic accuracy of PIGF, TC, and TG in predicting ICP was assessed via receiver operating characteristic curves. *P* values <.05 were considered statistically significant.

3. Results

A total of 433 pregnant women were included, of whom 167 were diagnosed with ICP after 24 weeks of pregnancy. There were no significant disparities in terms of age, gestational body mass index, pregnancy history, and number of deliveries between pregnant women with and without ICP (all $P > .05$). However, the pregnancy week at delivery was notably lower in women with ICP compared to those without (37.63 ± 1.45 vs 38.23 ± 1.59, $P < .001$). Among the biomarkers measured, the levels of TBA (2.50 [1.60, 3.80] vs 21.20 [14.10, 33.70], $P < .001$), TG (2.23 [1.77, 2.60] vs 3.48 [2.65, 4.15], $P < .001$), TC (3.84 [3.36, 5.15] vs 5.55 [4.10, 6.56], $P < .001$), and FBG (4.44 [4.20, 4.65] vs 4.61 [4.31, 4.86], $P < .001$) were significantly lower in pregnant women without ICP in contrast to those with ICP, whereas PIGF levels were notably higher in women without ICP compared to those with ICP (324.26 [137.56, 686.06] vs 64.76 [22.74, 131.23], $P < .001$; Table 1).

Multivariate logistic regression analysis revealed that several factors were significantly associated with ICP. These included the pregnancy week at delivery (OR = 0.823, 95% CI: 0.769–0.879, $P < .001$), serum PIGF levels (OR = 0.994, 95% CI: 0.992–0.996, $P < .001$), TC levels (OR = 1.955, 95% CI: 1.586–2.409, $P < .001$), and TG levels (OR = 3.786, 95% CI: 2.655–5.399, $P < .001$; Table 2).

Table 1

Comparison of clinical data between pregnant women with and without intrahepatic cholestasis of pregnancy.

Variables	Pregnant women without ICP (n = 266)	Pregnant women with ICP (n = 167)	*P* value
Age	30.59 ± 4.42	31.30 ± 4.54	.106
Pregnancy week at delivery	38.23 ± 1.59	37.63 ± 1.45	<.001
Number of pregnancies	2 (1, 2.25)	2 (1, 3)	.198
Number of deliveries	0 (0, 1)	0 (0, 1)	.051
Gestational BMI	26.38 ± 2.74	26.23 ± 3.01	.615
TBA	2.50 (1.60, 3.80)	21.20 (14.10, 33.70)	<.001
PIGF	324.26 (137.56, 686.06)	64.76 (22.74, 131.23)	<.001
TG	2.23 (1.77, 2.60)	3.48 (2.65, 4.15)	<.001
TC	3.84 (3.36, 5.15)	5.55 (4.10, 6.56)	<.001
FBG	4.44 (4.20, 4.65)	4.61 (4.31, 4.86)	<.001

BMI = body mass index, FBG = fasting blood-glucose, ICP = intrahepatic cholestasis of pregnancy, PIGF = serum placental growth factor, TBA = total bile acids, TC = serum total cholesterol, TG = serum triglyceride.

The predictive capabilities of PIGF, TG, and TC for ICP were assessed using the area under the curve (AUC). PIGF exhibited an AUC of 0.858 (95% CI: 0.822–0.893) with a sensitivity of 70.060% and a specificity of 89.850%. Similarly, the AUC for TG was 0.830 (95% CI: 0.788–0.871) with a sensitivity of 68.263% and a specificity of 89.098%. TC presented an AUC of 0.721 (95% CI: 0.670–0.772), with a sensitivity of 59.880% and specificity of 78.571%. Intriguingly, when PIGF and TG were combined, the AUC reached 0.891 (95% CI: 0.862–0.920), demonstrating a sensitivity of 76.048% and specificity of 84.586%. Nevertheless, combining PIGF, TG, and TC resulted in an even higher AUC of 0.922 (95% CI: 0.898–0.946), achieving a sensitivity of 86.228% and specificity of 82.331% (Table 3 and Fig. 1).

We further conducted a correlation analysis to assess the relationship between the diagnostic markers and ICP (Table 4). PIGF showed a negative correlation with ICP, though it was not statistically significant (r = –0.091, P = .242). Similarly, TG showed a negligible correlation with ICP (R = 0.006, P = .943). Notably, serum TC displayed a significant negative correlation with ICP (r = –0.224, P = .004). FBG presented a non-significant negative correlation (r = –0.052, P = .506). Moreover, the pregnancy week at delivery also showed a significant negative correlation with ICP (r = –0.184, P = .017).

4. Discussion

This study has demonstrated that PIGF, TC, and TG are independent risk factors for ICP. The combination of PIGF, TC, and TG holds the potential to predict the occurrence of ICP in pregnant women and establish a predictive foundation for this condition.

The placenta, serving as the central site for maternal-fetal nutrient exchange, has recently emerged as a focus of exploration in relation to ICP. Within the vascular endothelial growth factor family, PIGF plays a pivotal role, orchestrating endothelial cell proliferation, activation, migration, and anti-apoptosis. This orchestration is crucial for the appropriate development of the placental vasoganglion and the enhancement of vascular permeability.[21,22] However, prior research has primarily concentrated on identifying PIGF expression within placental tissues sourced from individuals with ICP, with no previous evaluations of PIGF levels in serum.[23] In our current study, it has been observed that serum PIGF levels among pregnant women afflicted with ICP were lower compared to those without the condition. This observation might be attributed to excessive maternal cholestasis leading to the constriction and spasm of placental villous blood vessels. Excessive bile salt deposition on the placental villi plate could result in chorionic edema and constriction of the intervillous space. These changes can ultimately lead to compromised placental perfusion, thereby manifesting as alterations in PIGF levels. In contrast to the primary focus of previous investigations on predicting pre-eclampsia and fetal growth restriction using PIGF,[24,25] our study provides an original contribution by establishing the predictive value of PIGF for ICP. Specifically, our study demonstrated an AUC of 0.858 for PIGF when employed for the distinct diagnosis of ICP. This was coupled with a sensitivity of 70.10% and specificity of 89.80%, thus addressing a significant gap in the predictive utility of PIGF in the context of ICP.

As far back as 1973, a cross-sectional study documented an established link between ICP and disrupted lipid profiles.[26] In a separate investigation, it was noted that maternal dyslipidemia exhibited heightened prominence within the severe ICP subgroup, implying that the severity of maternal dyslipidemia might be intricately tied to the degree of ICP severity.[27] Our current study aligns with these discoveries, as it identified elevated levels of TC and TG among pregnant women with ICP. The connection between ICP and maternal dyslipidemia can be elucidated by acknowledging the pivotal role assumed by TBA in lipid metabolism. Existing evidence underscores TBA influence over lipid production, lipoprotein excretion within the liver, plasma clearance, and intestinal cholesterol absorption. This regulatory role is primarily facilitated through the activation of farnesoid X receptor (FXR) and lipoprotein metabolism.[28,29] The multivariable regression analysis conducted within our study has unveiled the independent contributions of TC and TG towards the development of ICP. This concurs with the earlier investigation by Jin et al,[30] which highlighted a strong correlation between elevated TG levels in pregnant women during the latter stages of gestation and an augmented risk of gestational diabetes mellitus, pre-eclampsia, ICP, and other adversities. In tandem with these findings, the outcomes of a recent prospective, population-based study[31] also brought to light a positive association between total cholesterol concentration throughout pregnancy and low-density lipoprotein levels during the final 2 trimesters, indicative of the risk of developing ICP.

In contrast to the present study's focus on ICP during mid-to-late gestation, Zhang et al[32] employed alanine aminotransferase, glutamyl transpeptidase, fibrinogen, platelet large cell ratio, activated partial thromboplastin time, lactate dehydrogenase, creatinine, and mean corpuscular hemoglobin concentration levels to prognosticate ICP during the initial 20 weeks of gestation. An independent investigation by Dong et al[33] unveiled that a composite of L-palmitoyl carnitine, acyl CoA oxidase 1, and glycocholic acid levels holds potential as a biomarker ensemble for diagnosing and predicting ICP during the first and second trimesters. When juxtaposed with other biomarkers utilized for predicting and diagnosing

Table 2

Multivariable logistic regression analysis for ICP prediction during pregnancy.

Variables	OR	95% CI		*P* value
		Lower limit	Upper limit	
Age	1.026	0.964	1.093	.413
Pregnancy week at delivery	0.823	0.769	0.879	<.001
PIGF	0.994	0.992	0.996	<.001
TG	3.786	2.655	5.399	<.001
TC	1.955	1.586	2.409	<.001
FBG	1.118	0.976	1.281	.107

CI = confidence interval, FBG = fasting blood-glucose, ICP = intrahepatic cholestasis of pregnancy, OR = odds ratio, PIGF = serum placental growth factor, TC = serum total cholesterol, TG = serum triglyceride.

Table 3

Predictive significance of serum PIGF, TC, and TG in ICP.

Parameters	Sensitivity (%)	Specificity (%)	The best cutoff value	AUC	95% CI
PIGF	70.060	89.850	100.354	0.858	0.822–0.893
TG	68.263	89.098	3.075	0.830	0.788–0.871
TC	59.880	78.571	5.260	0.721	0.670–0.772
PIGF + TG	76.048	84.586	0.420	0.891	0.862–0.920
PIGF + TG + TC	86.228	82.331	0.355	0.922	0.898–0.946

AUC = area under the curve, CI = confidence interval, ICP = intrahepatic cholestasis of pregnancy, PIGF = serum placental growth factor, TC = serum total cholesterol, TG = serum triglyceride.

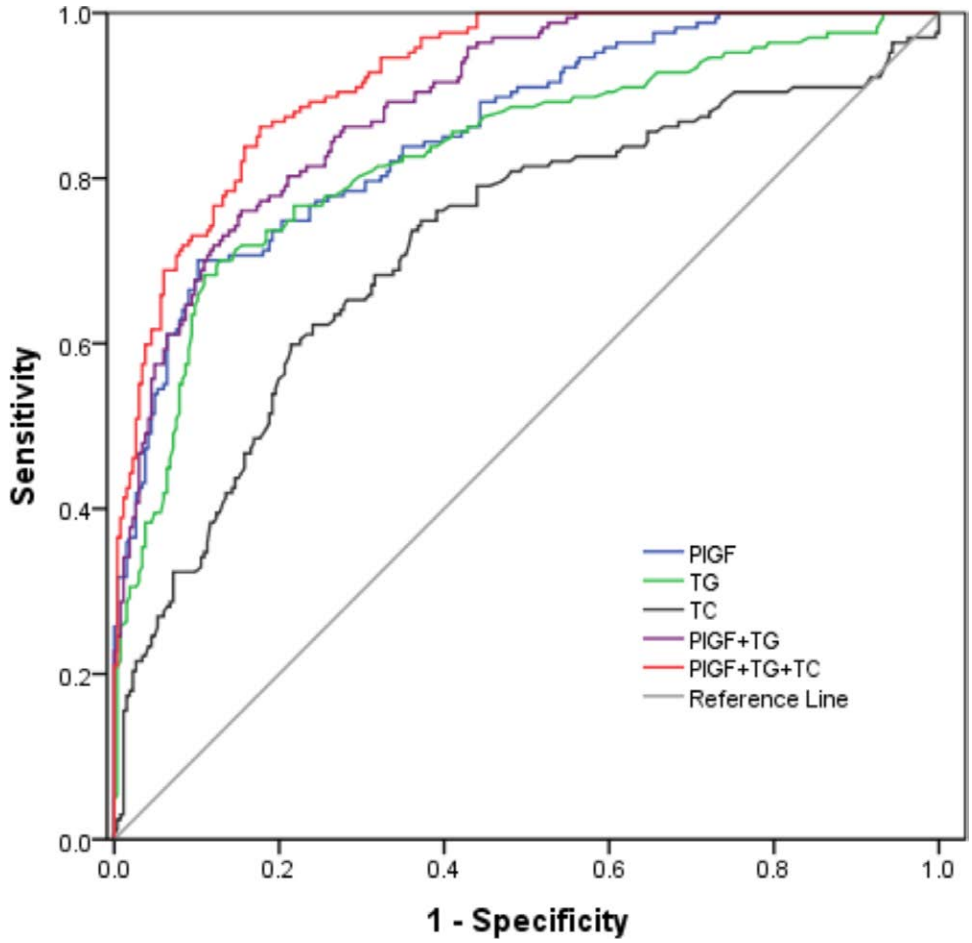

Figure 1. ROC curves of PIGF, TG, and TC in predicting ICP. PIGF = placental growth factor, ROC = receiver operating characteristic, TC = total cholesterol, TG = triglycerides.

Table 4

Correlation analysis of diagnostic markers and ICP.

Variables	*r*	*P* value
PIGF	−0.091	.242
TG	0.006	.943
TC	−0.224	.004
FBG	−0.052	.506
Pregnancy week at delivery	−0.184	.017

FBG = fasting blood-glucose, ICP = intrahepatic cholestasis of pregnancy, PIGF = serum placental growth factor, TC = serum total cholesterol, TG = serum triglyceride.

ICP, including leptin, adiponectin, apelin, and ghrelin,[34] the elevated receiver operating characteristic-AUC values generated by the synergistic use of PIGF, TC, and TG suggest that the amalgamation of these 3 metrics offers heightened precision in prognosticating ICP. Notably, the serological markers harnessed within this study are easily accessible and frequently assessed during routine outpatient or inpatient assessments.

Nonetheless, certain limitations persisted within this study. Firstly, the study was confined to a singular center, thereby necessitating an enlargement of the sample size to confer heightened reliability to the clinical trial data. Secondly, the intricate interplay of these factors, which collectively influence the onset of ICP, has not received exhaustive scrutiny and demands further investigation. Furthermore, the participants encompassed within the current study were exclusively singleton pregnant women, potentially rendering the study's findings less translatable to expectant mothers with multiple pregnancies.

To conclusion, the combination of PIGF, TC, and TG demonstrates a promising potential for predicting ICP in pregnant women. It is vital to underscore that these findings warrant validation through prospective, multicenter studies.

Author contributions

Conceptualization: Ping Li, Yurong Jiang, Yiping You.
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