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ORIGINAL ARTICLE

The *IDO* genetic polymorphisms and postpartum depressive symptoms: an association study in Chinese parturients who underwent cesarean section

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Abstract

Postpartum depressive symptoms (PDS) are not an uncommon mood disorder in postpartum women. Our previous research indicated a role for increased tryptophan (TRP) metabolism along the kynurenine pathway (KP) in the pathogenesis of PDS. Accordingly, this study was going to investigate the association of indoleamine-2,3-dioxygenase (IDO, a key enzyme of KP) genetic polymorphisms with PDS. Seven hundred twenty-five women receiving cesarean section were enrolled in this study. PDS was determined by an Edinburgh Postnatal Depression Scale (EPDS) score ≥ 13. Subsequently, 48 parturients with PDS and 48 parturients without PDS were selected for investigation of perinatal serum concentrations of TRP, kynurenine (KYN), and KYN/TRP ratio, the latter is the representative of IDO activity. In addition, seven single nucleotide polymorphisms of the IDO gene were examined. Following this genotyping, 50 parturients carrying the IDO rs10108662 AA genotype and 50 parturients carrying the IDO rs10108662 AC + CC genotype were selected for comparisons of TRP, KYN, and KYN/TRP ratio levels. This study showed the PDS incidence of 6.9% in the Chinese population, with PDS characterized by increased IDO activity ($p < 0.05$), versus women without PDS. We also found that the variations of IDO1 gene rs10108662 were significantly related to PDS incidence ($p < 0.05$). Furthermore, there was a significant difference in IDO activity between the IDO rs10108662 CA + AA, versus CC, genotypes. Our findings indicate a role of the kynurenine pathway in the development of PDS, rs10108662 genetic polymorphism resulting in changes of IDO activity might contribute to PDS pathogenesis.

Keywords Postpartum depressive symptoms · Cesarean · Parturients

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Introduction

Postpartum depressive symptoms (PDS) were first proposed as a mood disorder by Pitt in 1968 (Pitt 1968). It does not only interfere with mother-infant relationships but may also contribute to cognitive deficits and behavioral changes in infants (Guedeney et al. 2014; Surkan et al. 2016). The etiology and course of PDS have been investigated in recent decades. However, it cannot be accurately predicted or efficiently prevented, highlighting the need for useful biomarkers.

Over the past decade, research in depression more widely has shifted to an emphasis on the role of oxidative and nitrosative stress in association with changes in immune-inflammatory processes, especially alterations in the levels of kynurenine pathway activation (Anderson and Maes 2014). Increased kynurenine pathway activation lowers the plasma concentrations of serotonin and melatonin, while increasing kynurenine pathway products that have significant impacts on neuronal and immune cell functioning (Chopra et al. 2011; Anderson and Maes 2014). Recent work has proposed these pathways may be of some importance to pre- and postpartum depression (Roomruangwong et al. 2018).

Over 95% of tryptophan (TRP) in humans is metabolized along the kynurenine pathway (Maddison and Giorgini 2015). Indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) catalyze the conversion of TRP to kynurenine (KYN), which is further converted to a number of kynurenine pathway products, including kynurenic acid (KYNA) and quinolinic acid (QUIN), by kynurenine aminotransferase (KAT) and kynurenine-3-monoxygenase (KMO), respectively (Yi et al. 2015; Wang et al. 2017).

IDO is the main rate-limiting enzyme of the kynurenine pathway and is widely expressed in the brain, kidney, spleen, and other organs. It can be induced not only by pro-inflammatory cytokines but also by endotoxins and free radicals (Oxenkrug 2007; Qin et al. 2017; Zhang et al. 2015). Elevated IDO activity, by driving the kynurenine pathway, decreases serotonin and melatonin synthesis, thereby contributing to pathways classically linked to mood disorders. Clinical and basic studies consistently show increased IDO activity to be correlated with depression. Hepatitis C patients treated with interferon-α (IFN-α), an inflammatory cytokine, have an increased likelihood of developing depression, arising from the concurrent induction of IDO (Wichers et al. 2005). O'Connor et al. (2009) found that lipopolysaccharide (LPS)-induced depression-like behaviors in mice were associated with increased IDO activity, which was modulated by the inflammatory response, and were prevented by IDO inhibitors. Schrocksnadel and colleagues (Schröcksnadel et al. 2003) found an elevated KYN/TRP ratio (indicating IDO activity) in the blood plasma of parturients with PDS, which was correlated with levels of plasma immune-inflammatory markers, suggesting a role of perinatal inflammatory activity and the kynurenine pathway in perinatal depression.

Genetic factors are important in many diseases, including PDS (Mehta et al. 2012; Costas et al. 2010). Previously, we showed that KMO polymorphisms were correlated with PDS, implicating the kynurenine pathway in the genetic susceptibility to PDS (Wang et al. 2017). However, it requires investigation to whether IDO polymorphisms modulate PDS susceptibility, especially as the genetic modulation of IDO in preclinical models indicates a significant impact on systemic and central immune cell functioning (Gonzalez-Pena et al. 2016). Soichot et al. (2011) reported that the variable number tandem repeat (VNTR) polymorphisms in the promotor region of *IDO1* are involved in the modulation of tumor immunity. Smith and colleagues found that IDO mutations are associated with IFN-α-induced moderate and severe depressive symptoms (Smith et al. 2012). Given that the kynurenine pathway is associated with PDS and IDO is influenced by genetic factors, we hypothesize that there is an association between *IDO1* and *IDO2* with PDS, which is mediated through IDO activity, as indicated by a KYN/TRP ratio. In this study, seven single nucleotide polymorphisms (SNPs) of the IDO were screened (*IDO1* rs7840765, rs7820268, rs3739319, and rs10108662 and *IDO2* rs72632016, rs4503083, and rs4736794), and their association with the incidence of PDS after cesarean section was evaluated. Moreover, plasma concentrations of TRP and KYN in parturients were measured in order to delineate the role of the absolute levels and their ratio in the development of PDS.

Materials and methods

Participants and procedure

A total of 725 parturients, who underwent a cesarean section at the Third Xiangya Hospital of Central South University, were enrolled in this study. This project was approved by the ethics committee of Third Xiangya Hospital of Central South University (2014.1–2016.12), and all of the participants signed consent forms before delivery. Inclusion criteria were (1) aged > 18y, (2) pregnancy < 28w, (3) ASA (American Society of Anesthesiologists) grade II, (4) cesarean section, and (5) able to communicate with visitors (Pinsonneault et al. 2013; Wang et al. 2017).

Before and during *cesarean* section/surgery, parturients were physiologically monitored for heart rate, blood pressure, and oxygen saturation. Parturients received intraspinal anesthesia. They were given oxygen inhalation through a nasal catheter and were rehydrated intravenously. General sociodemographic data of each participant was collected using a self-designed questionnaire, including maternal age, full-term pregnancy or not, degree of stress during pregnancy

Table 1 Clinical characteristics and incidence of PDS

Factors		Non-PDS	PDS	*p* value
Age	≥ 35Y	108	9	0.714
	< 35Y	567	41	
Full-term pregnancy	Yes	599	44	0.876
	No	76	6	
Stress during pregnancy	Severe	19	8	< 0.001
	Moderate	291	29	
	Mild	365	13	
Education	College degrees or above	279	10	0.001
	High school or associate diploma	332	30	
	Junior middle school or below	64	10	
Accidental pregnancy	Yes	224	18	0.689
	No	450	32	
Conception method	Natural	626	44	0.224
	Artificial	49	6	
Employment	Yes	535	39	0.833
	No	140	11	
Income (CNY/monthly)	< 5000	13	2	0.642
	5000–10,000	93	6	
	> 10,000	569	42	

PDS, postpartum depressive symptoms; *CNY/monthly*, China Yuan monthly

(Chen et al. 1991), educational level, accidental pregnancy or not, conception method, employment status during pregnancy, and family income.

The PDS status was assessed using the total score of the Chinese-validated version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al. 1987). The EPDS was administered at the eighth week after delivery, based on a PDS onset definition of 6–8 weeks after delivery. A threshold score of ≥ 13 on the EPDS was applied to categorize parturients into the PDS group.

All blood samples were subjected to strict quality control prior to analysis, with any of the following leading to exclusion from further analysis: (1) participants with poor compliance, (2) samples that could have been contaminated during storage, (3) participants that left hospital having only completed the questionnaire, (4) changes in their conditions resulting in severe health complications, (5) outliers data, as measured by high performance liquid chromatography (HPLC) and mass spectrometry (MS), and (6) samples that had an influence on values of HPLC and MS. Furthermore, the exclusion criteria for both groups included a history of any neurologic, psychiatric or autoimmune disorders, currently receiving antipsychotic treatment, acute infection, concurrent serious medical condition, or drug and/or alcohol abuse within the past 6 months. Therefore, 48 parturients with PDS (EPDS score ≥ 13) and 48 postpartum controls (CP) (EPDS score ≤ 8) were selected.

Genotyping procedure of IDO polymorphisms

The *IDO1* (rs7840765, rs7820268, rs3739319, and rs10108662) and *IDO2* (rs72632016, rs4503083, and rs4736794) gene polymorphisms were chosen from the International Hapmap Project Phase II database of the Chinese population (http://www.hapmap.org/). Target SNP selection was performed using the Haploview software (version 4.2). All the target alleles had to meet the following criteria: having a frequency > 5% in the Chinese Han population and with clinical significance supported by previous studies showing significant impacts on IDO functioning (Lee et al. 2014). Before anesthesia, 2 ml peripheral venous blood was drawn and

Table 2 The change of TRP and KYN in women during perinatal period ($\bar{X} \pm SD$)

Index	The end of term	Postpartum day 1	Postpartum day 3
TRP (μg/ml)	3.6604 ± 0.9165	4.6687 ± 1.1416*	4.6933 ± 1.0698*
KYN (μg/ml)	0.1587 ± 0.0677	0.2281 ± 0.11225*	0.1974 ± 0.0723*

*$p < 0.05$ compared with the end of term

TRP, tryptophan; *KYN*, kynurenine

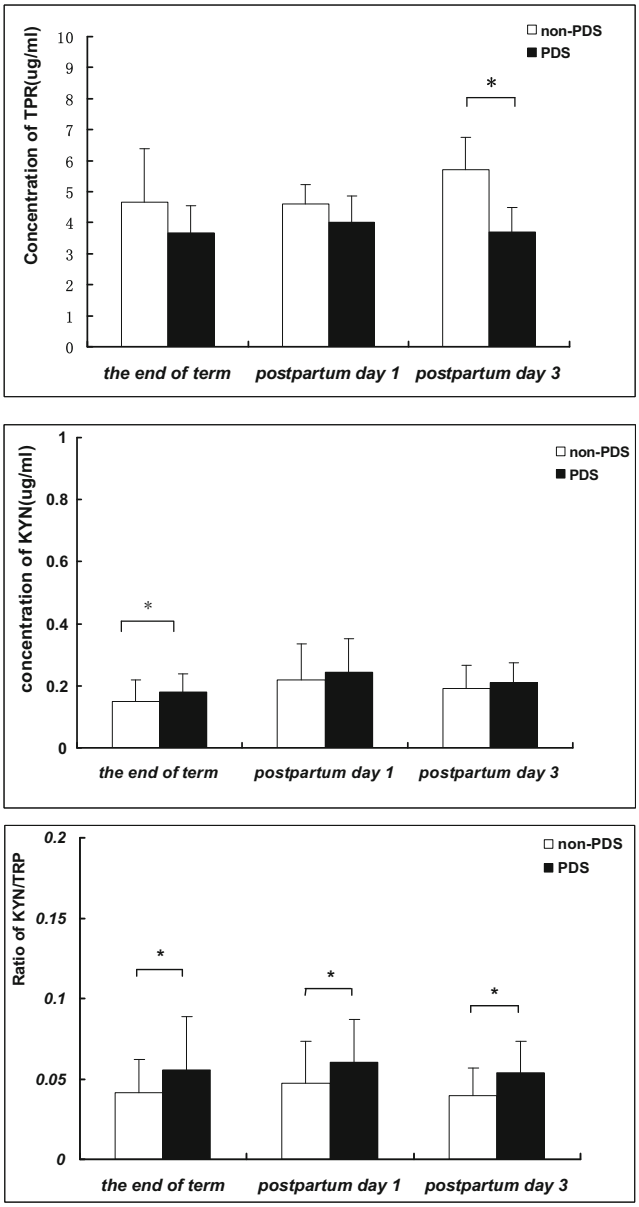

Fig. 1 The levels of TRP, KYN, and KYN/TRP ratio in women with or without PDS. *$p < 0.05$ compared with women without PDS. Error bars ± 1SD (standard deviation). TRP, tryptophan; KYN, kynurenine; PDS, postpartum depressive symptoms

collected in a test tube containing ethylene diamine tetraacetic acid (EDTA) anticoagulant and frozen at − 20 °C. The SQ Blood DNA extract kit was used to extract genomic DNA from the peripheral blood samples. The IDO alleles were screened by Haploview and referenced from previous publications. Sequenom Mass Array SNP (gene chip) was used to perform the genotyping (Bioyong Biological Technology Co., Ltd. Beijing).

Blood samples for determination of IDO activity were collected from 50 parturients carrying the IDO rs10108662 AA genotype and 50 parturients carrying the IDO rs10108662 AC + CC genotype. The exclusion criteria for both groups included a history of any neurologic, psychiatric or autoimmune disorders, current antipsychotic treatment, acute infection, concurrent serious medical condition, or drug and/or alcohol abuse within the past 6 months.

HPLC detection of TRP and KYN

Standard products of TRP and KYN were purchased from Sigma–Aldrich (Merck Corporation, Bedford, MA, USA). Standards and controls were established by adding defined volumes of the stock solutions to human plasma obtained from a blood bank. Quality control samples were generated in order to obtain low and high amounts of the analytes. HPLC-grade methanol and formic acid were purchased from Merck (Darmstadt, Germany). Water was deionized and filtered with a Milli-Q Plus apparatus (Merck Corporation, Bedford, MA, USA). The chromatographic column was VP-ODS, 250 × 4.6 mm (SHIMADZU, Japan). The mobile phase consisted of a solution of 0.1% aqueous formic acid (eluent A) and 100% of methanol (eluent B). Flow rate was set at 1.0 ml/min, and column temperature was set at 40.0 °C. The injection volume was 80 μl, and the total analysis run time was 15 min.

Blood samples were collected from 48 parturients with PDS and 48 parturients without PDS, 50 parturients carrying the IDO rs10108662 AA genotype and 50 parturients carrying the IDO rs10108662 AC + CC genotype. Plasma samples were taken before the operation, on postpartum day 1 and day 3. Samples were stored at − 80 °C until analysis. A volume of 200 μl plasma sample was mixed with 20 μl, 10% perchloric acid precipitant, followed by vortex for 30 s and centrifugation at 13200 g for 5 min, 100 μl of clean upper layer was transferred to a vial for the autosampler. Eighty microliter was injected into the chromatographic system (SHIMADZU LC-20A liquid chromatograph; CBM-20Alite system controller; LC-20AT infusion pump; CTO-20A column temperature box; SIL-20A automatic sampling device; SPD UV detector; LC solution Workstation). The plasma KYN/TRP ratio was calculated, with a higher ratio indicating an increase in IDO enzymatic activity (Laich et al. 2002; Wang et al. 2017).

Statistical analysis

IBM SPSS software (version 23.0) was used for statistical analysis. The collected variables and the incidence of PDS were compared by Chi-square tests. The Hardy–Weinberg equilibrium, linkage disequilibrium, and haplotype analysis were evaluated by SHEsis (http://analysis.bio-x.cn/myAnalysis.php) (Shi and He. 2005). The association study was analyzed in additive, dominant, and recessive models. An additive model was used for the additive

Table 3 Frequency of IDO gene polymorphisms in women with and without PDS

SNPs	Genotype	Non-PDS	PDS	Additive		Dominant		Recessive	
				OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
IDO1									
rs10108662	CC	390	40	Reference	0.006	0.343 (0.169–0.698)	0.002	0.927 (0.908–0.947)	0.101
	CA	246	10	0.396 (0.195–0.807)	0.009				
	AA	38	0	0.907 (0.880–0.935)	0.062				
rs7820268	CC	378	36	Reference	0.032	0.497 (0.263–0.938)	0.028	0.925 (0.906–0.945)	0.044
	CT	242	14	0.607 (0.321–1.150)	0.122				
	TT	54	0	0.913 (0.886–0.941)	0.014				
rs3739319	GG	124	10	Reference	0.293	0.902 (0.439–1.852)	0.778	0.594 (0.304–1.158)	0.123
	AG	316	28	1.099 (0.518–2.329)	0.806				
	AA	234	12	0.636 (0.267–1.513)	0.303				
rs7840765	TT	598	42	Reference	0.314				
	GT	76	8	1.499 (0.678–3.312)	0.314				
IDO2									
rs4736794	AA	260	14	Reference	0.289	0.165 (0.855–3.052)	0.137	1.435 (0.695–2.962)	0.326
	AG	314	26	1.538 (0.787–3.006)	0.205				
	GG	100	10	1.857 (0.799–4.318)	0.145				
rs4503083	TT	248	8	Reference	0.012	3.056 (1.412–6.615)	0.003	1.310 (0.636–2.699)	0.463
	AT	318	32	3.119 (1.412–6.890)	0.003				
	AA	108	10	2.870 (1.103–7.472)	0.025				
rs72632016	GG	666	50	Reference	1.000				
	AG	8	0	0.930 (0.912–0.949)	1.000				

PDS, postpartum depressive symptoms; *IDO*, indoleamine-2,3-dioxygenase; *SNPs*, single nucleotide polymorphisms; *OR*, odds ratio; *CI*, confidence interval

effects of the SNPs, with the direction of the regression coefficient representing the effect of each extra minor allele. Dominant and recessive models are tests for the minor allele with two of the classes pooled. Multiple logistic regression was utilized to perform multivariate association analysis. For variables with skewed distributions, we used the Mann–Whitney *U* test. Differences were considered statistically significant when $p < 0.05$.

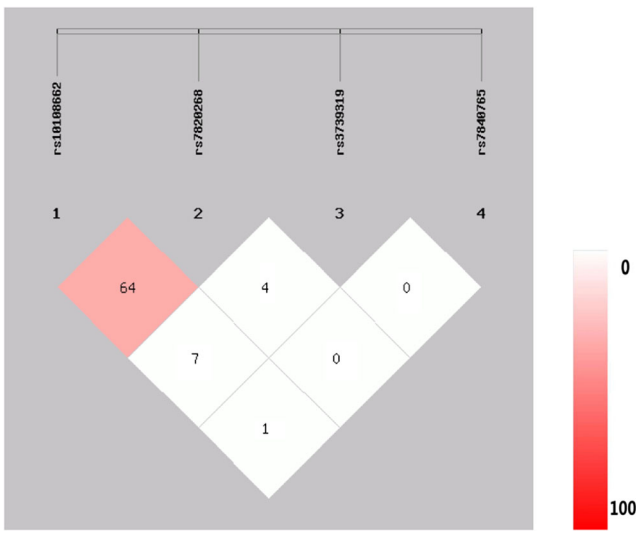

Fig. 2 Linkage disequilibrium test of *IDO1* locus rs7840765, rs7820268, rs3739319, and rs10108662. The white square in above figure represents the weaker linkage disequilibrium between the two loci, while the red represents stronger linkage disequilibrium between the two loci. IDO, indoleamine-2,3-dioxygenase

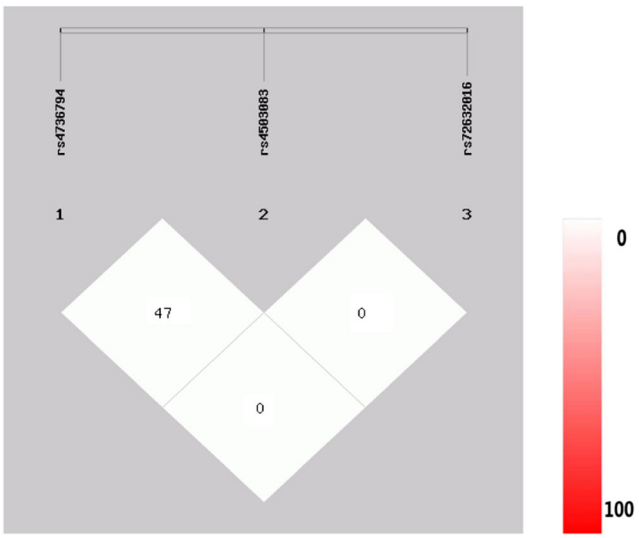

Fig. 3 Linkage disequilibrium test of *IDO2* locus rs72632016, rs4503083, and rs4736794. The white square in above figure represents the weaker linkage disequilibrium between the two loci, while the red represents stronger linkage disequilibrium between the two loci. IDO, indoleamine-2,3-dioxygenase

Table 4 Haplotype analysis of IDO1 gene locus and PDS

Haplotype	PDS (freq)	Non-PDS (freq)	χ^2	*p* value	OR (95% CI)
A T A T	10.00 (0.100)	245.68 (0.182)	4.904	0.026	0.477 (0.244–0.931)
A T G T	0.00 (0.000)	40.64 (0.030)	2.303	0.129	0.000 (0.000–0.008)
C C A G	5.40 (0.054)	52.80 (0.039)	0.429	0.512	1.354 (0.545–3.365)
C C A T	36.60 (0.366)	441.67 (0.328)	0.312	0.576	1.129 (0.737–1.729)
C C G T	41.40 (0.414)	452.94 (0.336)	1.838	0.175	1.334 (0.878–2.026)
C T G T	4.00 (0.040)	36.47 (0.027)	0.481	0.488	1.449 (0.505–4.154)

The haplotypes with frequencies less than 0.03 are not listed

PDS, postpartum depressive symptoms; *IDO*, indoleamine-2,3-dioxygenase; *OR*, odds ratio; *CI*, confidence interval; *freq*, frequency

Results

Clinical characteristics and PDS incidence

Data showed a PDS incidence rate of 6.9% from the 725 enrolled parturients undergoing cesarean section. The association between general sociodemographic data and PDS is summarized in Table 1. There were significant differences between groups with or without PDS regarding stress during pregnancy and education ($p < 0.05$).

Plasma concentrations of TRP, KYN, and IDO activity in parturient with or without PDS

As shown in Table 2, plasma concentrations of TRP and KYN on postpartum day 1 and day 3 were significantly higher than those at the end of term ($p < 0.001$). No differences in TRP levels were observed for parturients with PDS, versus parturients without PDS, at the end of term and postpartum day 1.

TRP levels in PDS, versus non-PDS, were lower on postpartum day 3 (3.69 ± 0.80 μg/ml vs 5.71 ± 1.04 μg/ml, $p < 0.001$). KYN levels in PDS, versus non-PDS, were higher at the end of term (0.18 ± 0.05 μg/ml vs 0.14 ± 0.04 μg/ml, $p = 0.045$), and there were non-significant trend increases in KYN levels at postpartum day 1 and day 3. The KYN/TRP ratios in PDS, versus non-PDS, were significantly higher at these same time points (0.06 ± 0.03 vs 0.04 ± 0.02, $p = 0.01$; 0.06 ± 0.02 vs 0.04 ± 0.02, $p = 0.020$; 0.05 ± 0.0195 vs 0.03 ± 0.01, $p = 0.004$). Such data indicated that parturients with, versus without PDS, had an enhanced level of IDO enzymatic activity (Fig. 1).

Association of IDO genetic polymorphisms with incidence of PDS

The IDO gene SNPs (rs7840765, rs7820268, rs3739319, rs72632016, rs10108662, rs4503083, and rs4736794) were obtained by the gene chip method. Frequencies of those IDO gene SNPs are listed in Table 3. The genotype distributions of these SNPs are in concordance with the Hardy–Weinberg equilibrium. The genotype proportions were as follows: *IDO1* rs10108662 (CC, CA, AA): 59.4%, 35.4%, 5.2%; rs7820268 (CC, CT, TT): 57.2%, 35.4%, 7.4%; rs3739319 (GG, AG, AA): 18.5%, 47.5%, 33.9%; rs7840765 (TT, GT): 88.4% and 11.6%, respectively. *IDO2* rs4736794 (AA, AG, GG): 38.6%, 46.6%, 14.8%; rs4503083 (TT, TA, AA): 36.8%, 47.2%, 16.0%; rs72632016 (GG, AG): 98.8% and 1.2%, respectively. Three SNPs were significantly associated with PDS incidence. Specifically, rs10108662 and rs4503083 were related to the incidence of PDS in both additive ($p = 0.006$ and $p = 0.012$, respectively) and dominant ($p = 0.002$ and $p = 0.003$, respectively) models; rs7820268 was significant in the additive ($p = 0.032$), the dominant ($p = 0.024$), and the recessive ($p = 0.044$) models (Table 3).

The linkage disequilibrium and haplotype analysis of the *IDO1* (rs7840765, rs7820268, rs3739319, and

Table 5 Haplotype analysis of IDO2 gene locus and PDS

Haplotype	PDS (freq)	Non-PDS (freq)	χ^2	*p* value	OR (95% CI)
A A G	8.22 (0.082)	110.02 (0.082)	0.000	0.998	1.001 (0.478–2.097)
A T G	45.78 (0.458)	717.53 (0.532)	2.251	0.133	0.733 (0.487–1.101)
G A G	43.78 (0.438)	422.61 (0.314)	6.372	0.011	1.691 (1.120–2.551)
G T G	2.22 (0.022)	89.84 (0.067)	3.132	0.076	0.315 (0.082–1.215)

The haplotypes with frequencies less than 0.03 are not listed

PDS, postpartum depressive symptoms; *IDO*, indoleamine-2,3-dioxygenase; *OR*, odds ratio; *CI*, confidence interval; *freq*, frequency

Table 6 Multivariable analysis of variation of IDO gene and the incidence of PDS

SNPs	B	S.E.	Wald	*p* value	Exp (B)
rs10108662	− 1.524	.572	7.093	0.008	.218
rs7820268	.791	.523	2.288	0.130	2.206
rs3739319	.236	.323	.531	0.466	1.266
rs7840765	.473	.428	1.219	0.269	1.604
rs4736794	.221	.320	.479	0.489	1.248
rs4503083	1.063	.550	3.736	0.053	1.758

IDO, indoleamine-2,3-dioxygenase; *PDS*, postpartum depressive symptoms; *SNPs*, single nucleotide polymorphisms; *B*, regression coefficient; *S.E.*, standard error; *Exp (B)*, odds ratio

rs10108662) and *IDO2* (rs72632016, rs4503083, and rs4736794) gene loci were carried out by SHEsis software, and $r^2 > 0.8$ was used as the dividing line of linkage disequilibrium. The results showed that there was no linkage disequilibrium among the *IDO1* (Fig. 2) or *IDO2* (Fig. 3) SNPs. The results also showed that *IDO1* gene ATAT haplotype (Table 4) and the *IDO1* gene GAG haplotype (Table 5) were related to the incidence of PDS ($p = 0.026$ and $p = 0.011$, respectively).

As shown in Table 6, multivariable analysis of variation in the IDO gene and the incidence of PDS showed that the rs10108662 polymorphism was the most significant SNP ($p = 0.008$), the incidence of PDS in parturients carrying the *IDO1* rs10108662 CC genotype was higher than that in parturients carrying the *IDO1* rs10108662 CA + AA genotype (Table 3).

The rs10108662 and IDO activity

Since *IDO1* gene rs10108662 was most strongly correlated with PDS, we investigated the plasma TRP and KYN concentration and KYN/TRP ratio in parturients carrying distinct genotypes of rs10108662 (Fig. 4). There was no significant association between IDO rs10108662 and plasma TRP levels during the perinatal period. The KYN level in parturients carrying the IDO rs10108662 CA + AA, versus CC, genotype was lower at the end of term (0.16 ± 0.07 μg/ml vs 0.25 ± 0.02 μg/ml, $p < 0.001$), and there was a non-significant trend decrease in KYN levels between the two groups on postpartum day 1 and day 3. Of note, the KYN/TRP ratio was significantly lower in CA + AA carriers than that in CC carriers, at the three time points indicated above (0.04 ± 0.00 vs 0.07 ± 0.00, $p < 0.001$; 0.05 ± 0.01 vs 0.06 ± 0.02, $p = 0.016$; 0.04 ± 0.01 vs 0.05 ± 0.00, $p = 0.009$). These results suggest that the alteration in IDO activity may be due to variations in the IDO rs10108662 C/A SNP.

Discussion

The major findings in this study were as follows: (1) IDO polymorphisms are associated with the incidence of PDS, which might be ascribed to altered IDO activity induced by distinct rs10108662 genotypes; (2) parturients carrying the CC genotype in rs10108662 (IDO1) had a higher risk for PDS, as compared to parturients carrying an AC or AA

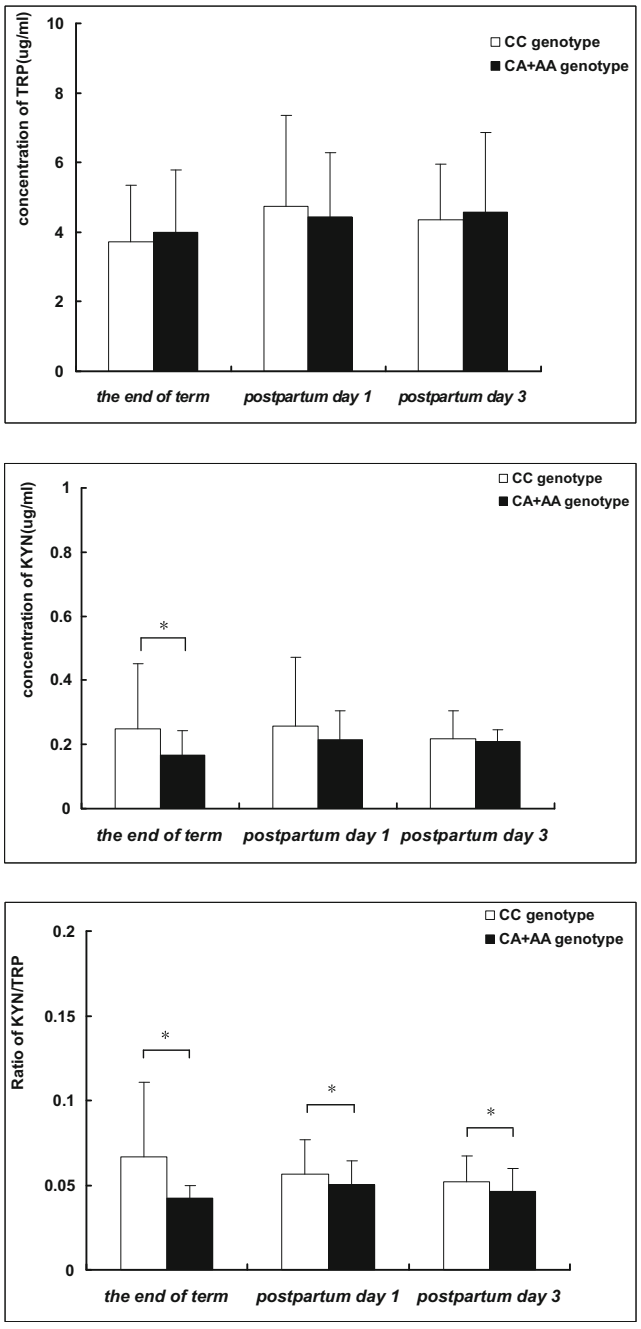

Fig. 4 Plasma concentrations of TRP, KYN, and KYN/TRP ratio in parturients carrying different *IDO1* rs10108662 genotypes. *$p < 0.05$ compared with the end of term. Error bars ± 1SD (standard deviation). TRP, tryptophan; KYN, kynurenine; IDO, indoleamine-2,3-dioxygenase

genotype; and (3) psychosocial stress and lower education increase PDS risk.

The reports about the relationship between the mode of delivery and postpartum depression are controversial (Xu et al. 2017), but in order to avoid more clinical confounding and be convenient for sample collection, the present study selected parturients undergoing cesarean section to study the relevance between the kynurenine pathway and PDS.

The kynurenine pathway is the major metabolic pathway of TRP. TRP is first converted to KYN in this pathway. KYN is often an intermediate product, with its plasma concentration providing an indicant of the proportion of TRP metabolized through the kynurenine pathway (Németh et al. 2005; Lovelace et al. 2017). Moreover, KYN is able to cross the blood-brain barrier via neutral transporters, with about 60% of central KYN being peripherally derived (Gál and Sherman 1980; Schwarcz et al. 2012). Plasma KYN may therefore be an important indicant of peripheral and central TRP metabolism and kynurenine pathway activity. The KYN/TRP ratio is widely used as an indicator of IDO activity in basic and clinical research (Lancellotti et al. 2011; Watanabe et al. 1980; Miller et al. 2004). Our data showed that the plasma KYN concentration after delivery was significantly increased. Further analysis revealed that IDO activity was significantly higher in perinatal parturients with PDS than that in those without PDS. These results suggest that TRP metabolism through the kynurenine pathway was enhanced during the perinatal period, especially in parturients with PDS, and support the hypothesis that increased IDO activity has the potential to induce PDS by breaking the metabolic balance with TRP.

Genetic factors can also play an important role in the pathophysiology of PDS. Figueiredo et al. (2015) reviewed the correlation between genetic factors and PDS incidence, concluding that multiple gene mutations were associated with PDS. In the current study, we analyzed the influence of IDO polymorphisms on PDS occurrence, finding that PDS incidence was significantly lower in parturients carrying the IDO1 rs10108662 CA or AA genotype compared to that in parturients carrying the *IDO1* rs10108662 CC genotype. We also measured the perinatal IDO activity in parturients with distinct rs10108662 genotypes, showing that CA and AA carriers had significantly reduced IDO activity and lower perinatal plasma KYN concentrations compared with CC carriers. These results strongly support a role for genetic factors in PDS susceptibility and pathophysiology by the modulation of IDO activity. Increased IDO activity in the perinatal period enhances kynurenine pathway activity at the expense of the serotonin and melatonin pathways, with consequences for wider neuronal and immune system regulation. The rs10108662 is located in intron 7 of the *IDO1* gene and thus not translated into a protein, but our data showed that C > A mutation of IDO rs10108662 was associated with a reduced IDO and kynurenine pathway activity during the perinatal period, which may reduce PDS incidence. Such data indicates that further research on IDO and its genetic variations will be useful to clarify its role in the etiology, course, and management of PDS.

A series of previous studies have shown that environmental factors can modulate PDS occurrence (Bernazzani et al. 1997; Da Costa et al. 2000). Our data indicates a role for psychosocial stress and lower education in PDS risk. Although such data may indicate a role for psychotherapy in off-setting PDS risk, it is also of note that prenatal diet may be of relevance, given that recent work showed probiotics and improvement of gut microbiome during pregnancy decreased the likelihood of PDS as well as postpartum anxiety (Slykerman et al. 2017; Anderson 2018).

One limit of this study is the small sample size. Given the growing appreciation of the role of wider organs and tissues in the etiology of mood disorders, it also requires clarification as to where such genetic susceptibility factors may be acting. As to how the C > A mutation of IDO rs10108662 alters IDO catalytic activity, and the underlying mechanisms, remains to be determined in future research.

In summary, this study investigated PDS occurrence in parturients that underwent cesarean section and the association of IDO polymorphisms with plasma concentrations of TRP and KYN. Our findings indicate that PDS was associated with significantly increased IDO activity and an enhanced KYN/TRP ratio. IDO polymorphisms were correlated with PDS, and this correlation may be due to altered IDO activity. Our results suggest that inhibiting overactivation of the kynurenine pathway may prove of clinical utility in PDS. The relevant aspects of the kynurenine pathway, such as QUIN-driven excitotoxicity at the *N*-methyl-*D*-aspartate receptor, and site of relevance, such as the gut, immune system, and/or brain, require further investigation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the declaration of Helsinki (World Medical Association 2013) using procedures that were approved by the ethics committee of Third Xiangya Hospital of Central South University.

Statement of informed consent Informed consent was obtained from all individual participants included in the study.

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