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Clinical correlation and prognostic value of xanthine and inflammatory factors in postpartum depression

Lizhen Zhang[1], Bo Zhou[1], Peter Wang[2], Lilu Shu[2]

[1]Ningxiang People Hospital, Ningxiang, China
[2]Zhejiang Zhongwei Medical Research Center, Hangzhou, China

ABSTRACT

Objectives: As a common postpartum complication, postpartum depression is an important social and health problem. Postpartum depression causes many changes in relevant indicators, such as inflammatory factors and thyroid hormones. However, the effects of inflammatory factors, thyroid hormones and xanthine on postpartum depression have not yet been fully elucidated. Therefore, it is of great clinical significance to clarify the changes in the key indicators of postpartum depression.

Material and methods: A total of 139 pregnant women were included in this study. Finally, only 56 patients completed the Edinburgh Depression Scale (EPDS) evaluation and blood sample collection.

Results: In the current study, 34 (60.7%) patients were normal, 10 (17.9%) women were depressive tendency and 12 (21.4%) women developed depression. Among the serum indexes detected, the expression levels of thyroid function indexes T3, T4 and TSH, and inflammatory factors, such as hs-CRP, IL-1β, IL-6 and TNF-α, in the EPDS ≥ 9 group were slightly higher than those in the normal group (EPDS < 9). Xanthine levels in the depression group (EPDS ≥ 13) were significantly higher than normal group (EPDS < 9).

Conclusions: Our findings suggest that xanthine levels in patients with postpartum depression were increased significantly, but there were no significant changes in thyroid function and some inflammatory indexes. Therefore, timely detection and intervention of maternal xanthine may help reduce the incidence of postpartum depression.

Keywords: postpartum depression; EDS; thyroid function; inflammatory factors; xanthine; IL-6; EPDS

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INTRODUCTION

Depression is a disease that affects the body, mood and thinking in human [1]. It can also affect eating and sleeping rules, people feelings and ways of thinking [2]. For women, pregnancy not only produces physiological changes in various systems, but also leads to corresponding psychological changes, which often leads to mental disorders, especially depression [3]. Postpartum depression is a common postpartum complication, which is mainly manifested in maternal irritability, fear, timidity, emotional instability, uneasiness, anxiety, depression and excessive concern about their own and infant health during the puerperium [4, 5]. It usually starts within two weeks after giving birth and gradually worsens. It is obvious at 4 ~ 6 weeks after birth and can recover by itself within 3 ~ 6 months, but some parturients can last for 1~2 years [6]. The incidence rate of postpartum depression is approximately 10%~18% and has been increasing year by year. The incidence of postpartum depression in the second child is 1.5 times higher than that in the first child [7, 8]. The occurrence of postpartum depression seriously affects the physical and mental health of pregnant women and is not conducive to the growth and development of newborns. It is an urgent problem to be concerned and should be solved by the society at present.

Many studies have shown that postpartum depression is related to inflammatory response [9]. The inflammatory factors often include IL-6, hs-CRP, TNF-a and IL-1b [10, 11]. The pregnancy process is an noninflammatory state, showing an increase in pro-inflammatory factors in the third trimester of pregnancy [12]. Dowlati et al. [13] found that patients with major depression had higher levels of TNF-α and IL-6 than patients without depression. In recent studies on perinatal

Corresponding author:
Peter Wang or Lilu Shu
Zhejiang Zhongwei Medical Research Center, No. 452, Sixth Street, 310018 Hangzhou, China
e-mail: wangpeter2@hotmail.com; or shulilu12345@126.com

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depression, it was found that pro-inflammatory biomarkers IL-6, IL-1β, TNF-α and CRP were associated with depressive symptoms, anxiety and mood disorders [14–16]. However, the effects of inflammatory factors on postpartum depression are quite different, suggesting that it needs to be further clarified [17]. Studies have also revealed that changes in thyroid hormones can lead to postpartum depression [18, 19]. The homeostasis of thyroid hormones during pregnancy is challenged due to adaptive changes in the hypothalami pituitary thyroid (HPT) axis [20]. In addition, the increase of estrogen concentration in pregnant women leads to the sharp increase of serum concentration of thyroid binding globulin, which affects the increase of total triiodothyronine (TT3) and total tetraiodothyronine (TT4) [21]. Thyrotropin (TSH) is decreased at the beginning of pregnancy and is increased again at the end of pregnancy, reaching the antenatal concentration, and then usually remains stable throughout pregnancy [18, 22]. One study has proposed that the large release of xanthine leads to anxiety [23]. However, there is still insufficient evidence about the changes of thyroid hormone and the occurrence of postpartum depression.

Postpartum depression changes some relevant indicators. However, there are still some problems about the relationship between inflammatory factors, thyroid hormone and xanthine on the short-term and long-term effects of postpartum depression. Clarifying the changes of key indicators of postpartum depression and drug intervention will more effectively help pregnant women out of depression, which has important clinical significance. This study explored multi-dimensional indicators for detection and comparison, such as thyroid function indicators, inflammatory factors and xanthine. Moreover, we collected clinical information of patients, including maternal age, fetal sex and feeding mode, and conducted relevant analysis, trying to find the key factors leading to postpartum depression, to provide evidence support for the clinical intervention of patients with postpartum depression.

MATERIAL AND METHODS

Patient inclusion and ethical approval

Inclusion criteria: 1. Pregnant women aged 18 and above; 2. Within 20 weeks of pregnancy; 3. The current residence is more than 1 year, and there is no long-term relocation plan in other areas within the next 1 year; 4. Birth check-up and delivery in our hospital; 5. Sign informed consent. Exclusion criteria: 1. Previous history of mental disorders; 2. Have a history of serious central nervous system diseases; 3. Suffering from serious physical diseases; 4. Have a history of psychoactive drug abuse.

Pregnant women who came to Ningxiang people's Hospital from 2020 to 2021 were selected to collect the basic information of patients and completed the self-rating depression scale (SDS) before 20 weeks of pregnancy. If the prenatal SDS score is ≥ 53, it will be excluded and will not participate in the follow-up study. Clinical registration has been carried out and the registration number is 2021001.

Study design and scoring criteria

The puerperal women who met the above criteria were evaluated by Edinburgh Depression Scale (EPDS) at 42 days after delivery, and blood samples were collected. The serums were separated after centrifugation at 3000 r/min for 4 min. The serum levels of triiodothyronine (T3), tetraiodothyronine (T4) and TSH were measured by enzyme-linked immunosorbent assay. Immunoturbidimetry on automatic biochemical analyzer was used to detect interleukin-1 β (IL-1β), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and xanthine levels. All operations were carried out in strict accordance with the operating steps in the kit instructions.

For SDS, the cut-off value of SDS standard score is 53 points, of which 53–62 points are mild depression, 63––72 points are moderate depression, and more than 73 points are severe depression. All subjects are scored with EPDS self-rating scale, which includes 10 items, and each item is divided into four levels: never 0, occasionally 1, often 2, always 3, with a total score of 0–30. If the total score of EPDS is less than 9, it is normal and 10 ~12 points are the tendency of postpartum depression, and the total score ≥ 13 points can be diagnosed as postpartum depression. The higher the total score, the more serious the degree of depression.

Data statistical analysis

SPSS 21.0 software was used for statistical analysis of the data. The measurement data in line with normal distribution were expressed by mean standard deviation. Independent sample t-test was used for comparison between groups, and χ^2 was used for comparison between counting data groups. Pearson correlation analysis was used for the correlation between EPDS score and laboratory test indexes. The difference was statistically significant with $p < 0.05$.

RESULTS

The incidence rate of postnatal depression in women

A total of 139 pregnant women agreed and participated in this study. Incomplete records of basic information, incomplete SDS score, prenatal SDS ≥ 53 score and loss of blood sample records were excluded. The last 56 participants conducted this follow-up study (Fig. 1). The average age (± SD) of these 56 pregnant women was 27.3 ± 4.8 years. According to the EPDS score, the patients were divided into normal group (EPDS < 9), depression tendency group (9 ≤ EPDS < 13) and depression group (EPDS > 13). Five days after delivery, 10 of the 56 pregnant women had depression tendency, and

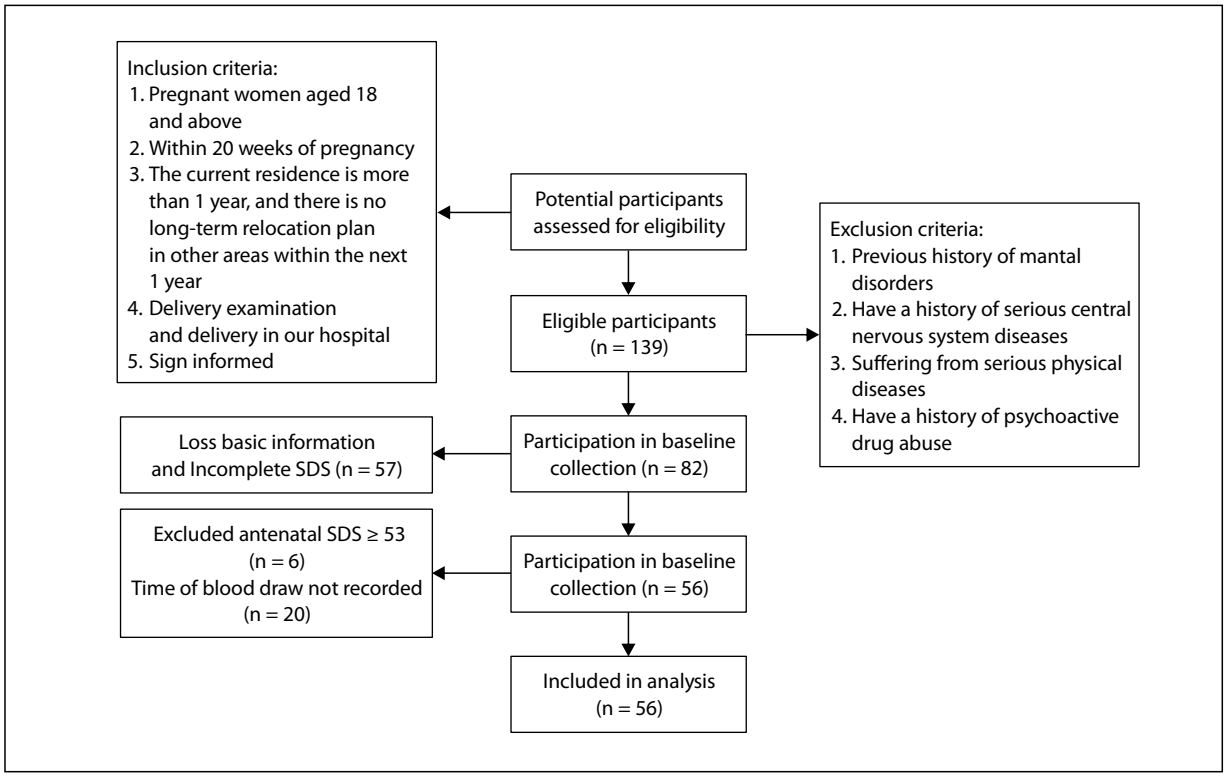

Figure 1. Consort flow diagram is illustrated; SDS — self-rating depression scale

Table 1. Basic data of pregnant women in each group

	EPDS < 9	9 ≤ EPDS < 12	EPDS ≥ 13	p value
Number (56)	34 (60.7%)	10 (17.9%)	12 (21.4%)	/
Age	27.3 ± 4.6	26.6 ± 6.2	27.7 ± 4.7	> 0.05
Feeding mode				
Breast feeding	12	3	4	/
Artificial feeding	2	4	1	/
Mix feeding	20	3	7	/
Infant gender satisfaction				
Yes	34	10	12	/
No	0	0	0	/

EPDS — Edinburgh Depression Scale

12 had depression. In our study group, the incidence rate of postnatal depression was 21.4% (Tab.1). The difference in age, feeding pattern and gender satisfaction of the three groups was not significant ($p > 0.05$) (Tab. 1).

Triiodothyronine (T3), tetraiodothyronine (T4) and thyrotropin (TSH) in the serum of pregnant women with depression

At 42 days postpartum, the thyroid function indexes T3, T4 and TSH in the serum of pregnant women with EPDS ≥ 9, including postpartum depression tendency and postpartum depression, were slightly higher than those in the normal group (EPDS < 9), but there was no significant difference between these two groups ($p > 0.05$) (Tab. 2). Further detections found that the inflammatory factors and hs-CRP in the serum of the depression groups were lower than those in the normal control group. The levels of IL-1 β, IL-6 and TNF-α were higher than that in the normal control group, but there was no significant difference between these two groups ($p > 0.05$) (Tab. 3).

Table 2. Comparison of thyroid function indexes

	EPDS < 9	EPDS ≥ 9	p value
Serum T3 [ng/dL]	1.63 ± 0.13	1.71 ± 0.18	0.2
Serum T4 [mg/dL]	0.90 ± 0.11	0.96 ± 0.16	0.32
Serum TSH [mU/L]	1.19 ± 0.56	1.39 ± 0.50	0.37

EPDS — Edinburgh Depression Scale; T3 — triiodothyronine; T4 — tetraiodothyronine; TSH — thyrotropin

Table 3. Comparison of inflammatory factor test results

	EPDS < 9	EPDS ≥ 9	p value
Serum hs-CRP [mg/mL]	18.90 ± 6.60	17.68 ± 3.90	0.61
Serum IL-1β [pg/mL]	2.36 ± 0.74	2.49 ± 0.42	0.62
Serum IL-6 [pg/mL]	15.65 ± 13.06	22.37 ± 27.14	0.43
Serum TNF-α [pg/mL]	7.66 ± 1.70	8.57 ± 1.95	0.23

EPDS — Edinburgh Depression Scale; CRP — C-reactive protein

Xanthine levels were higher in the serum of pregnant women with depression

As mentioned above, we analyzed the xanthine in the serum of pregnant women in EPDS ≥ 9 and EPDS < 9 groups. We found that the xanthine value in EPDS ≥ 9 group was higher than that in the normal group, and the p value was 0.09, which was close to 0.05. Moreover, we systematically analyzed the data of xanthine and found that the xanthine value in the depression group (9 ≤ EPDS < 13) was higher than that in the normal group (EPDS < 9), but there was no significant difference between these two groups ($p > 0.05$). The xanthine value in the depression group (EPDS ≥ 13) was also higher than that in the depression tendency group (9 ≤ EPDS < 13). Similarly, there was no significant difference between these two groups ($p > 0.05$). The xanthine value in the depression group (EPDS ≥ 13) was significantly higher than that in the normal group (EPDS < 9), and the difference between these two groups was statistically significant ($p < 0.05$) (Tab. 4 and 5).

DISCUSSION

Postpartum depression is a common and serious mental disorder, with a worldwide incidence rate of 13% ~ 19% [24]. This disease usually has a latent onset and is not easy to find. When the symptoms are mild to moderate and the behavior of seeking help is discouraged and diluted, postpartum depression can develop into severe and may even lead to suicide [25]. Postpartum depression is a serious risk to mothers and infants because it can lead to maternal mental disorders, infanticide and even suicide. Moreover, it has a significant negative impact on the mother infant relationship, the infant emotional, behavioral and cognitive development [26, 27]. Children with postpartum depression are more likely to have behavioral and emotional problems, which should be highly valued by clinical psychiatrists and obstetricians [28]. Therefore, early detection, early prevention and timely treatment are the main methods to treat postpartum depression, and exploring the etiology of postpartum depression is the key to prevention and treatment.

Edinburgh Depression Scale score is one of the most widely used postpartum depression screening scales at home and abroad, including mood, fun, self-blame, anxiety, fear, insomnia, coping ability, sadness, crying and self-injury [29]. Within 6 weeks postpartum, the total score of EPDS below 9 is normal, and the score of 9~12 is postpartum depression, which needs attention, follow-up and re-evaluation in the near future. Postpartum depression can be diagnosed if the total score is ≥ 13 [30]. There was no significant difference in age, feeding mode and satisfaction with fetal gender among the three groups ($p > 0.05$).

Postpartum depression is the result of multiple factors such as biological factors and social psychological factors [31]. The results of this study demonstrated that the thyroid function indexes T3, T4 and TSH in the EPDS ≥ 9 group were slightly higher than those in the normal group (EPDS < 9). There was no significant difference between these two groups, which was consistent with the clinical study that thyroxine could not correct postpartum depression. Changes in the immune system, especially inflammatory cytokines, play an important role in postpartum depression. IL-1β, IL-6 and hs-CRP are pro-inflammatory cytokines, which play an important role in the occurrence and development of immunity and inflammation [32, 33]. Our results showed that compared with the control group, the hs-CRP, IL-1β,

Table 4. Comparison of xanthine test results

	EPDS < 9[1]	EPDS ≥ 9[2]	
		9 ≤ EPDS < 12[3]	EPDS ≥ 13[4]
Serum xanthine (mean ± SD) [pmol/L]	393.61 ± 154.63	496.93 ± 116.57	
		442.32 ± 142.59	551.55 ± 52.76
p value	/	0.09[12]	
	0.55[13]	0.15[34]	0.04[41]*

EPDS — Edinburgh Depression Scale; SD — standard deviation; [1]represent EPDS < 9; [2]represent EPDS ≥ 9; [3]represent 9 ≤ EPDS < 12; [4]EPDS ≥ 13; [41]there is statistical significance between EPDS ≥13 groups and EPDS < 9

Table 5. Xanthine in postpartum depression test results

	Number	Age	Serum xanthine (mean ± SD)
EPDS < 9	34	27.29 ± 4.64	374.35 ± 108.65
EPDS ≥ 13	12	27.67 ± 4.74	549.53 ± 40.76
p value	/	0.9	0.03*

EPDS — Edinburgh Depression Scale; SD — standard deviation;
*represent statistical significance

IL-6 and TNF-α levels in maternal serum with EPDS ≥ 9 group were slightly higher, but there was no statistically significant difference. Therefore, the specific mechanism of serum inflammatory factors in the pathogenesis of postpartum depression still needs to expand the number of samples for further research and exploration.

Stress interferes with immune cells and affects the abnormal metabolism of immune cells, resulting in anxiety and depression [23]. Studies have shown that in animal models, stress interference leads to the rupture of T cell mitochondria and an increase of xanthine level, while xanthine acts on the amygdala and leads to mental problems [23]. The systematic analysis of xanthine data in this study found that the xanthine value of depression prone group (9 ≤ EPDS < 13) was higher than that of normal group (EPDS < 9), and the xanthine value of depression group was also higher than that of depression prone group, but there was no statistical significance between these two groups ($p > 0.05$). The xanthine value of depression group was significantly higher than that of normal group. This shows that the increase of xanthine may lead to the occurrence of postpartum depression. In the follow-up, we will further expand the number of samples to clarify the effect of xanthine on postpartum depression and provide new directions and ideas for clinical intervention of postpartum depression.

CONCLUSIONS

In conclusion, xanthine levels in patients with postpartum depression were increased significantly, and thyroid function indexes and some inflammatory indexes did not change significantly. The follow-up timely detection and intervention of maternal xanthine may help to reduce the incidence of postpartum depression and benefit the health of mothers and infants. Altogether, the xanthine level could be useful as an indicator of the risk of postpartum depression.

Article information and declarations

Data availability statement

The data are available from the corresponding author upon reasonable request.

Ethics statement

The study was approved by the Ethical Committee of Ningxiang people's Hospital.

Author contributions

L.Z. designed this study, performed the experiment and drafted the manuscript. B.Z. and P.W. searched for the literature and made the figures and tables. L.S. drafted the manuscript, designed this study and supervised this work. All authors approved the final manuscript.

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Not applicable.

Conflict of interest

None.

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