Journal of Psychosomatic Obstetrics & Gynecology

ISSN: 0167-482X (Print) 1743-8942 (Online) Journal homepage: https://www.tandfonline.com/loi/ipob20

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To cite this article: Asuka Hirose, Masakazu Terauchi, Tamami Odai, Kiyoko Kato & Naoyuki Miyasaka (2020): Depressive symptoms at postpartum are associated with those at the second trimester of pregnancy and the antioxidant activity immediately after delivery, Journal of Psychosomatic Obstetrics & Gynecology, DOI: 10.1080/0167482X.2019.1709817

To link to this article: https://doi.org/10.1080/0167482X.2019.1709817

Published online: 06 Jan 2020.

JOURNAL OF PSYCHOSOMATIC OBSTETRICS & GYNECOLOGY
https://doi.org/10.1080/0167482X.2019.1709817

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ARTICLE

Depressive symptoms at postpartum are associated with those at the second trimester of pregnancy and the antioxidant activity immediately after delivery

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ABSTRACT

Objective: This study aimed to investigate whether depressive symptoms at postpartum are associated with oxidative stress and antioxidant activity, as well as the symptoms during pregnancy.

Methods: This longitudinal study enrolled 84 women in their second trimester of pregnancy. Their depressive symptoms were assessed using Edinburgh postnatal depression scale (EPDS), and their oxidative stress and antioxidant activity were assessed using reactive oxygen metabolites/8-hydroxy-2′-deoxyguanosine and biological antioxidant potential (BAP) at around 26 and 36 weeks (time points 1 and 2) of gestation, and 3–6 days and 1 month (time points 3 and 4) postpartum. We evaluated the associations between EPDS at time point 4 and various parameters at the other time points.

Results: Multiple regression analysis revealed that EPDS at time point 1 (adjusted odds ratio: 1.06 per 0.1 point increase; 95% confidence interval [CI]: 1.03–1.11) and BAP at time point 3 (adjusted odds ratio: 0.93 per 10 μmol/L increase; 95% CI: 0.87–0.97) were independent predictors of EPDS at time point 4.

Conclusion: Depressive symptoms at the second trimester of pregnancy and the antioxidant activity immediately after delivery could predict postpartum depression.

TRIAL REGISTRATION: UMIN-CTR UMIN000022367

ARTICLE HISTORY
Received 2 October 2019
Revised 20 December 2019
Accepted 23 December 2019

KEYWORDS
Oxidative stress; antioxidant activity; Edinburgh postnatal depression scale; BAP; d-ROM; 8-OHdG

Introduction

Postpartum depression (PPD) is a type of mood disorder associated with childbirth. The prevalence of PPD varies depending on the definition of the disorder and diagnostic tools, and a review showed that it differs between 0.5 and 60% among countries [1]. In Japan, the incidence rates of mental disorders-III-revised (DSM-III-R) major depressive episode during pregnancy and within 3 months after delivery are 5.6 and 5.0%, respectively [2]. PPD has negative effects on raising children and can lead to maternal suicide; it also has consequences on the child's development. A systematic review revealed that the health of infants and children is closely associated with the health of their mothers and that maternal PPD decreases the quality of the home environment, maternal sensitivity and caregiving [3]. While the exact cause of PPD is unclear, it is believed to be a combination of physical and emotional factors, including hormonal changes [4], sleep deprivation [5] and past history of depression [6].

Many middle-aged women suffer from various menopausal symptoms, including depression. We previously demonstrated that depressive symptoms in middle-aged women are associated with oxidative stress [7]. PPD and perimenopausal depression are related to each other. For example, the history of PPD has been demonstrated to be associated with subsequent perimenopausal depression [8]. Furthermore, perinatal women experience drastic changes in their hormones and environments, which are also common in the perimenopausal period. These similarities raise the possibility that PPD may be also associated with oxidative stress.

This study aimed to investigate whether postpartum depressive symptoms are associated with oxidative stress and antioxidant activity, as well as the symptoms during pregnancy. It also aimed to

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determine parameters that are useful for the prediction of postpartum depressive symptoms.

Materials and methods

Design

This prospective analysis was conducted at the Department of Perinatal and Women's Medicine of Tokyo Medical and Dental University Hospital between October 2016 and December 2018. We included pregnant women who came to our hospital before 24 weeks of gestation. The exclusion criteria were as follows: refusal to give informed consent and not giving birth at our hospital. The study protocol was reviewed and approved by the Tokyo Medical and Dental University Review Board, and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki [9].

Protocol

At the enrollment, age, body composition, past medical history, complications that require a hospital visit, and lifestyle factors, such as working, exercising regularly, smoking and drinking alcohol, were evaluated. At around 26 weeks (time point 1) and 36 weeks (time point 2) of gestation, and 3–6 days (time point 3) and 1 month (time point 4) after delivery, we assessed body composition, psychological symptoms, sleep disorder, oxidative stress markers and antioxidant activity marker.

Measures

Depressive symptoms were assessed using the Edinburgh postnatal depression scale (EPDS). The EPDS, originally developed in the United Kingdom in 1987, is a 10-item self-report measure designed to screen women for symptoms of emotional distress during the postpartum period by using a 4-point Likert scale [10]. It has been translated into many languages and is now widely used worldwide. The cutoff scores vary across countries, although those for probable and possible depression scores have been suggested at 12/13 and 9/10, respectively, in the original version [10]. EPDS was translated into Japanese in 1996, and its reliability and validity were confirmed [11]. In the Japanese version, the total score of 9 or more is regarded as positive, suggesting probable depression. In the present study, we also defined an EPDS score of 9 or more as the presence of depressive symptoms.

Sleep disorder was evaluated using the Athens insomnia scale (AIS), which was developed as a brief and easy to administer questionnaire for determining the severity of insomnia defined according to the International Classification of Disease Tenth Revision [12]. The utility in clinical practice and research and reliability were confirmed previously [13].

The severity of oxidative stress and antioxidant activity were quantified by measuring the concentration of specific biomarkers. We evaluated serum diacron reactive oxygen metabolites (d-ROM) and urine 8-hydroxy-2′-deoxyguanosine (8-OHdG) as oxidative stress markers, and serum biological antioxidant potential (BAP) as an antioxidant stress marker. The d-ROM test is based on the capacity of a plasma sample to oxidize the chromogen substrate to its radical cation, and the test results are expressed as Carratelli units (CARR U) [14]. It was experimentally established that 1 CARR U corresponds to 0.08 mg of H_2O_2/dL, and the normal value in healthy subjects is between 250 and 300 CARR U. 8-OHdG is an oxidized derivative of a nucleoside deoxyguanosine, reflecting DNA oxidation [15,16]. Excreted in urine unmetabolized, it can be measured in urine samples noninvasively. The concentrations of 8-OHdG (ng) and creatinine (mg) were measured by immunochromatography using an automatic analyzer (ICR-001; Techno Medica, Tokyo, Japan), and 8-OHdG levels were corrected by creatinine (ng/mg creatinine). BAP test is based on the ability of a plasma sample to reduce ferric (Fe^{3+}) iron to its colorless ferrous (Fe^{2+}) derivative [14], and the result of which is an expression of total antioxidant activity. The concentrations of reduced ferric ions are determined by photometrically assessing the intensity of decoloration. The normal value of BAP is >2200 μmol/L [14]. The levels of d-ROM and BAP were measured using the FREE Carrio Duo system (Diacron International, Grosseto, Italy) according to the manufacturer's instructions.

Statistical analyses

The levels of oxidative stress markers and antioxidant activity markers during pregnancy, and the changes before and after delivery were initially evaluated. Next, by dividing into two groups according to EPDS scores at time point 4 as low (<9 points) and high (≥ 9 points), we compared background characteristics and various parameters at time points 1–3 between the two groups using univariate analyses (unpaired *t*-test,

Mann–Whitney test, and Fisher's exact test), and identified the factors associated with high EPDS at time point 4. Variables emerging with possible prognostic value for high EPDS at time point 4 were then entered into a multiple logistic regression analysis to detect parameters that were independently associated with high EPDS at time point 4.

Statistical analyses were performed using GraphPad Prism version 5.02 (GraphPad Software, San Diego, CA) and JMP version 11.0.0 (SAS Institute Inc, Cary, NC). A p-value < 0.05 was considered significant.

Results

A total of 126 pregnant women were recruited into the study. Forty-two (33.3%) patients dropped out of the study because of refusal to participate, declining participation during the study, or unobtainable data. Therefore, 84 women completed the study. Background characteristics are shown in Table 1.

The transition of oxidative stress markers during pregnancy and postpartum is shown in Figure 1. Compared with the level at time point 4, d-ROM at time points 1–3 and 8-OHdG at time points 1 and 3 were higher, and BAP at time points 1–3 was significantly lower. Moreover, as compared with the normal ranges in a population of healthy subjects of d-ROM and BAP (as mentioned above, 250–300 CARR U and $>2200\,\mu$mol/L, respectively), the levels of d-ROM at time points 1–3 were much higher and those of BAP were lower, and these results indicate that pregnant women probably have higher oxidative stress and lower antioxidant activity.

We divided the women into two groups according to the score of EPDS 9 or more and assessed background characteristics, various parameters at time points 1–3 and pregnancy complications between the two groups using univariate analyses (Tables 2 and 3). Sixty-nine women had a low EPDS score and 15 had a high score. We assessed background characteristics, and the women in the high EPDS group at time point 4 tended to have a higher prematernal body mass index (Table 2). We then assessed various parameters at time points 1–3 and pregnancy complications and found significant differences between groups in EPDS at time points 1–3; AIS at time points 1 and 3; and body weight, body mass index, 8-OHdG and BAP at time point 3 (Table 3). Only the BAP at time point 3 was lower in women in the high EPDS group at time point 4, and all the other parameters were higher.

Variables emerging with possible prognostic value for high EPDS scores at time point 4 were then entered into a multiple logistic regression analysis (Table 4). Consequently, EPDS at time point 1 and BAP at time point 3 were independent predictors to high EPDS at time point 4 (Table 4). The adjusted odds ratios to be classified in the high EPDS group at time point 4 were 1.06 per 0.1 point increase in EPDS score at time point 1 (95% confidence interval [CI]: 1.03–1.11) and 0.93 per 10 μmol/L increase in BAP at time point 3 (95% CI: 0.87–0.97).

Table 1. Background characteristics of the participants ($n = 84$).

	Mean ± SD	Number	(%)
Age (years)	33.4 ± 4.9		
Gravida (*n*)	1.9 ± 0.9		
Para (*n*)	0.51 ± 0.68		
Height (cm)	159.6 ± 5.2		
Weight (kg)	54.3 ± 8.0		
BMI (kg/cm^2)	21.3 ± 3.1		
Past history (yes/no)		14/70	16.7
History of depressive disorder (yes/no)		3/81	3.6
Complication (yes/no)		21/63	25.0
Fertility treatments (yes/no)		22/62	26.2
Working (yes/no)		56/28	66.7
Quit job during pregnancy (yes/no)		18/66	21.4
Exercising regularly (yes/no)		9/75	10.7
Smoking (prematernal) (yes/no)		9/75	10.7
Passive smoking (yes/no)		17/67	20.2
Alcohol (yes/no)		34/50	40.5

BMI: body mass index.

Discussion

In this prospective analysis, we found that oxidative stress was higher and antioxidant activity was lower during pregnancy and immediately after delivery. Depressive symptoms at postpartum were also associated with those in the second trimester and the antioxidant activity immediately after delivery, suggesting that the marker and the symptom could be useful for the prediction of PPD. This study is the first to reveal the association between postpartum depressive symptoms and antioxidant activity.

Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant activity [17]. ROS change lipids, proteins and DNA and cause damage to cells and tissues. Previous studies reported that oxidative stress has an influence on cancer [18], inflammation [19], atherosclerosis [20,21], myocardial infarction [21], inflammatory airway diseases [22] and age-related illnesses [23]. A meta-analysis revealed an association between oxidative stress and depression in the general population [24] and showed that patients with depression have higher oxidative stress and lower antioxidant status.

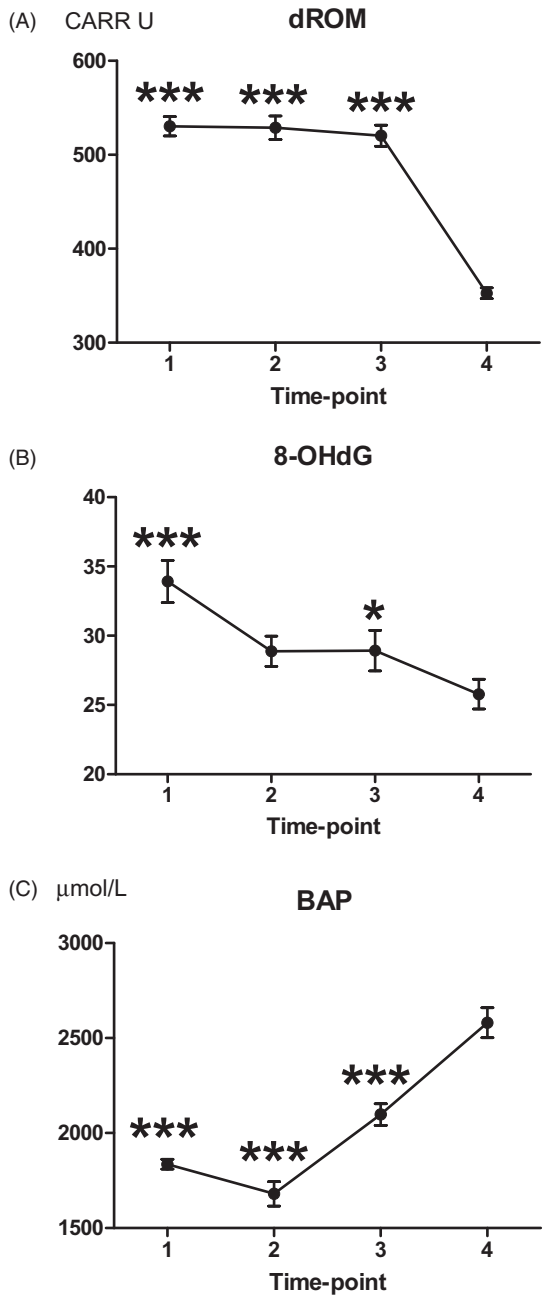

Figure 1. Transition of oxidative stress markers during pregnancy and postpartum. *Student's *t*-test, $p < 0.05$ vs. time point 4; ***Student's *t*-test, $p < 0.001$ vs. time point. CARR U: Carratelli units; d-ROM: diacron reactive oxygen metabolites; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; BAP: biological anti-oxidant potential.

With regard to oxidative stress during pregnancy, a previous study demonstrated that several oxidative stress markers, such as urine 8-OHdG, serum 8-isoprostane, total antioxidant capacity, glutathione peroxidase and superoxide dismutase, increase in the third trimester and return to non-pregnant levels postpartum [25], as with our study. In addition, pregnancy complications, including preeclampsia [26], gestational diabetes mellitus [27], fetal growth restriction and spontaneous pregnancy loss, are associated with oxidative stress [28]. Oxidative stress has been speculated to be detrimental to pregnancy, but a recent animal study has shown that ROS-mediated signaling may be essential for maintaining placental angiogenesis in preeclampsia [29]. Further studies are necessary to confirm the influence of oxidative stress on pregnancy.

In our study, the levels of d-ROM at time points 1–3 were considerably higher than the normal range, compared with BAP. Pregnancy may affect oxidative stress rather than antioxidant activity. Therefore, the individual potential to counterbalance oxidants may be important to not get depressed, and this may lead to the association of only the BAP at time point 3 with PPD.

A meta-analysis revealed the association between depression and oxidative stress among patients with depression [24], but the period between the changes of markers in oxidative stress and antioxidant activity and the exacerbation and remission of depression remains unclear. Considering together with our results that markers had not returned to normal range level at time point 3, it might require some time to falter the oxidative stress influence on pregnancy. The impact of low antioxidant activity at time point 3 might have appeared about a few months later.

The EPDS at time point 1 was associated with that at time point 4. A previous study assessed depression and anxiety during pregnancy and 1 month after delivery. It demonstrated that depressive symptoms are common during the first trimester of pregnancy (25%) and in postpartum (17%) [30]. Pregnant women may be less likely to feel depressed when they are facing childbirth, and evaluating psychological symptoms from the beginning of pregnancy is important.

Limitations and strengths

This study has two limitations: (1) the number of participants was relatively small; and (2) the participants were healthy women, most of whom did not have high EPDS at time point 4. Further studies with a larger sample including women with depressive symptoms or past history of depression are warranted to corroborate our findings.

By contrast, our study has two strengths: (1) unlike previous studies, parameters were assessed at 3–6 days after delivery; therefore, the differences between immediately after delivery and one month after delivery became clear; and (2) the measurements of d-

Table 2. Comparison of background characteristics between the low and high EPDS groups at time point 4 using univariate analyses.

	Low EPDS (<9 points, $n = 69$)		High EPDS (≥9 points, $n = 15$)		
	Mean ± SD	(%)	Mean ± SD	(%)	*p*-Value
Age (years)	33.8 ± 4.9		31.9 ± 4.4		0.17[a]
Gravida (*n*)	1.9 ± 1.0		1.9 ± 0.7		0.95[b]
Para (*n*)	0.52 ± 0.71		0.47 ± 0.50		0.94[b]
Height (cm)	159.8 ± 5.1		158.7 ± 5.2		0.46[a]
Weight (kg)	53.6 ± 7.8		57.7 ± 8.2		0.07[a]
BMI (kg/cm^2)	21.0 ± 3.1		22.9 ± 2.7		0.03[a]
Past history		18.8		6.7	0.45[c]
Past history of depressive disorder		1.4		13.3	0.08[c]
Complication		24.6		26.7	1.00[c]
Fertility treatments		30.4		6.7	0.10[c]
Working		69.6		53.3	0.24[c]
Quit job during pregnancy		20.3		26.7	0.73[c]
Regular exercise		8.7		20.0	0.20[c]
Smoking (prematernal)		10.1		13.3	0.66[c]
Passive smoking		23.2		6.7	0.29[c]
Alcohol		42.0		33.3	0.58[c]

EPDS: Edinburgh postnatal depression scale; BMI: body mass index. [a]Unpaired *t*-test. [b]Mann–Whitney test. [c]Fisher's exact test.

Table 3. Comparison of various parameters at time points 1–3 between the low and high EPDS groups at time point 4 using univariate analyses.

	Low EPDS (<9 points, $n = 69$)	High EPDS (≥9 points, $n = 15$)	
	Mean ± SD	Mean ± SD	*p*-Value
Time point 1			
Weight (kg)	59.5 ± 8.0	61.9 ± 7.8	0.29[a]
BMI (kg/cm^2)	23.3 ± 3.2	24.6 ± 2.5	0.16[a]
EPDS (points)	2.9 ± 3.0	9.3 ± 3.3	<0.001[b]
AIS (points)	4.2 ± 2.7	6.3 ± 3.4	0.02[b]
d-ROM (CARR U)	534.9 ± 98.6	509.5 ± 58.6	0.35[a]
8-OHdG	35.2 ± 13.5	27.7 ± 10.8	0.07[a]
BAP (μmol/L)	1839.2 ± 231.0	1821.9 ± 256.3	0.80[a]
Time point 2			
Weight (kg)	63.0 ± 8.2	64.3 ± 10.8	0.64[a]
BMI (kg/cm^2)	24.7 ± 3.4	25.6 ± 3.6	0.44[a]
EPDS (points)	9.0 ± 3.3	14.4 ± 3.5	<0.001[b]
AIS (points)	5.6 ± 3.2	5.9 ± 2.8	0.73[b]
d-ROM (CARR U)	529.2 ± 109.8	526.4 ± 99.0	0.94[a]
8-OHdG	29.2 ± 9.7	27.5 ± 6.9	0.57[a]
BAP (μmol/L)	1701.1 ± 593.5	1568.3 ± 255.1	0.45[a]
Time point 3			
Weight (kg)	59.3 ± 7.7	63.1 ± 9.6	0.11[a]
BMI (kg/cm^2)	23.3 ± 3.2	25.0 ± 3.1	0.06[a]
EPDS (points)	3.6 ± 3.5	11.0 ± 4.9	<0.001[b]
AIS (points)	6.9 ± 3.8	10.1 ± 3.9	<0.01[b]
d-ROM (CARR U)	520.0 ± 96.8	522.5 ± 100.9	0.93[a]
8-OHdG	27.3 ± 9.6	35.9 ± 19.5	0.02[a]
BAP (μmol/L)	2165.3 ± 514.0	1798.6 ± 141.3	0.01[a]

EPDS: Edinburgh postnatal depression scale; BMI: body mass index; AIS: Athens insomnia scale; d-ROM: diacron reactive oxygen metabolites; CARR U: Carratelli units; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; BAP: biological anti-oxidant potential. [a]Unpaired *t*-test. [b]Mann–Whitney test.

Table 4. Factors associated with high EPDS at time point 4 (≥9 points) according to multiple logistic regression analysis.

	Crude OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
BMI	1.16 (0.67–2.47)	0.58		
EPDS (time point 1)[a]	1.16 (1.02–1.89)	<0.01	1.06 (1.03–1.11)	<0.001
AIS (time point 1)[a]	0.88 (0.49–1.02)	0.10		
EPDS (time point 2)[a]	0.98 (0.90–1.04)	0.58		
EPDS (time point 3)[a]	1.04 (0.99–1.16)	0.15		
AIS (time point 3)[a]	1.16 (1.02–2.01)	<0.01		
8-OHdG (time point 3)	0.89 (0.59–1.16)	0.41		
BAP (time point 3)[b]	0.90 (0.64–0.98)	<0.01	0.93 (0.87–0.97)	<0.001

OR: odds ratio; CI: confidence interval; BMI: body mass index; EPDS: Edinburgh postnatal depression scale; AIS: Athens insomnia scale; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; BAP: biological anti-oxidant potential. [a]Per 0.1 point increase. [b]Per 10 μmol/L increase of BAP.

ROM, BAP and 8-OHdG are simple, inexpensive and practical because the results are obtained in about 10–15 min. Our results can be immediately used clinically.

Conclusion

Depressive symptoms in the second trimester of pregnancy and the antioxidant activity immediately after delivery could predict PPD.

Disclosure statement

MT received an unrestricted research grant from Kikkoman Corporation. No potential conflict of interest was reported by the other authors.

Funding

This work was supported by Japan Society for the Promotion of Science KAKENHI Grant Number [17K16835].

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➤ Current knowledge on the subject

- In Japan, the incidence rates of Diagnostic and statistical manual of mental disorders-III-revised (DSM-III-R) major depressive episode during pregnancy and within 3 months after delivery are 5.6 and 5.0%, respectively.
- The exact cause of postpartum depression (PPD) is unclear, but it is believed to be a combination of different factors.
- A meta-analysis revealed an association between oxidative stress and depression in the general population and showed that patients with depression have higher oxidative stress and lower antioxidant status.

➤ What this study adds

- We investigated the association between postpartum depressive symptoms and oxidative stress/antioxidant activity, and the parameters that are useful for the prediction of PPD.
- We found that oxidative stress was higher and antioxidant activity was lower during pregnancy and immediately after delivery.
- Depressive symptoms at postpartum were associated with those in the second trimester and the antioxidant activity immediately after delivery, suggesting that the serum biological anti-oxidant potential (BAP) and the Edinburgh postnatal depression scale (EPDS) score in the second trimester could be useful for the prediction of PPD.