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The Impact of Maternal Prenatal Depressive Symptoms and Anxiety on Infant Birth Weight in Japanese Primiparous Women

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ABSTRACT

Introduction: Depressive symptoms and anxiety are the most common mental health problems during pregnancy. The purpose of the present study was to investigate the association between each trimester's maternal depressive symptoms, anxiety, and infant birth weight.

Methods: We recruited pregnant women in their second trimester. Participants' blood and saliva were collected in the second trimester to investigate plasma cortisol and saliva oxytocin levels. Participants completed self-reported questionnaires that included the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Inventory (STAI) in the second and third trimesters. Hierarchical multiple linear regression was conducted using stepwise selection.

Results: Eighty-one primiparas participated in the study. As the results of linear regression showed, gestational age, hypertensive disorders of pregnancy, weight gain during pregnancy, and depressive symptoms in the third trimester were associated with infant birth weight. Depressive symptoms in the third trimester predicted lower infant birth weight. In contrast, depressive symptoms in the second trimester, state anxiety, and trait anxiety in both the second and third trimesters did not predict infant birth weight. Similarly, maternal plasma cortisol and saliva oxytocin levels were not related to infant birth weight.

Conclusion: Maternal depressive symptoms in the third trimester predicted lower infant birth weight. Mental health care for depressive symptoms in late pregnancy might be important for infant birth weight increases.

Keywords: *Depressive symptoms; Anxiety; Cortisol; Oxytocin; Birth weight*

BACKGROUND

Depressive symptoms and anxiety are the most common mental health problems during pregnancy. The prevalence of prenatal depressive symptoms was estimated at 9.1-17.2% in western countries (Straub et al., 2012; Bowen et al., 2012; Jairaj et al., 2019). It was higher in Asian countries, ranging from 14.4-26.3% (Ishikawa et al., 2011; Choi et al., 2014; Tsao et al., 2016). Globally, the incidence of prenatal anxiety ranged from 7.9% to 26.0% (Teixeira et al., 2009; Nasrean et al., 2010; Inabez et al., 2012; Bayrampour et al., 2015).

Some reviews found that prenatal depressive symptoms or anxiety are related to preterm birth or low birth weight (Staneva et al., 2015; Rose et al., 2016). Preterm birth and low birth weight cause several problems in infants (Saigal et al., 2008; Makhoul et al., 2009). In Japan, the preterm birth rate was 5.7%, and the low birth weight rate was 9.4% in 2017 (Mother's & Children's Health Organization, 2019). In other developed countries, these rates were approximately 7-12% and 6-8%, respectively (United Nations, 2020). Despite the low premature birth rate, the low birth weight rate in Japan is higher than that in other countries and needs to be reduced.

There is no consensus on the period in which maternal depressive symptoms or anxiety affect infant birth weight. Many previous studies have examined depressive symptoms or anxiety at only once in pregnancy (Nordeng et al., 2012; Chang et al., Nasreen et al. 2019; Dowse, 2020). In addition, several researchers have reported these associations without a defined period (Field et al., 2010; Flynn et al., 2015; Yang et al., 2017). Further research is needed in this direction.

Previous studies have investigated cortisol in pregnancy as a biomarker of maternal stress, depressive symptoms, and anxiety (Kramer et al, 2009; Cho et al, 2017; Duffy et al, 2018; Bandoli et al, 2018). Cortisol is the most important glucocorticoid produced by the hypothalamus-pituitary-adrenal axis (Levine et al., 2007). A systematic review suggested that hypercortisolemia is linked to transient depressive states, while hypocortisolemia is related to chronic depression in the pregnancy and postpartum period (Seth et al., 2016). Oxytocin is an important hormone in birth and lactation and is synthesized in specialized cells in the paraventricular and supraoptic nuclei of the hypothalamus (MacDonald and MacDonald, 2010). It reduces HPA axis responses and limbic reactivity to social stressors (Heinrichs et.al, 2008). In a systematic review of the perinatal period, six studies reported that mothers with higher oxytocin levels presented fewer depressive symptoms compared to mothers with lower oxytocin levels (Moura et al. 2016). The research with these biomarkers might allow a more multidimensional survey.

Researchers have examined the association between maternal depressive symptoms, anxiety, and infant birth weight. Nevertheless, the consensus on the period is lacking, and few studies have investigated biomarkers.

OBJECTIVE

The purpose of the present study is to investigate the association between each trimester's maternal depressive symptoms, anxiety, and infant birth weight. We also examined whether prenatal maternal cortisol levels or oxytocin levels predict infant birth weight.

METHODS

Participants and procedure

The present study was part of a longitudinal observational study. We recruited women in the second trimester of pregnancy at a hospital in Kyoto, Japan, from April 2018 to September 2019. The inclusion criteria were (a) primipara, (b) singleton pregnancy, (c) pregnant less than 22-week gestational age, (d) 20-40 years old, and (e) Japanese. The exclusion criteria were having (a) chronic diseases such as essential hypertension, diabetes type 1 and type 2, (b) mental diseases such as schizophrenia, and epilepsy, and (c) fetal disorder. After obtaining informed consent, research nurses collected the participants' saliva and blood in the second trimester. Participants completed self-reported questionnaires in the second and third trimesters. The questionnaires gathered data on maternal characteristics, depressive symptoms, and anxiety. The researcher reviewed their medical records after childbirth.

Based on the sample size calculation, we recruited 150 primiparas. One hundred thirty five primiparas participated in the study. Fourteen participants were transferred to other hospitals during pregnancy. Seventeen participants did not complete all questionnaires or sample collections. Furthermore, 23 participants' oxytocin assays were not performed correctly. Finally, 81 participants were included in this study.

Measures

Maternal demographic and pregnancy characteristics

Maternal information was collected from questionnaires, such as maternal age, education, marital status, and household income. Pregnancy information was obtained from medical records, such as fertility treatment, pre-pregnancy body mass index (BMI), weight gain during pregnancy, diagnosed hypertensive disorders of pregnancy (HPD), diagnosed gestational diabetes mellitus (GDM), mode of delivery, gestational age, and infant birth weight. Pre-pregnancy BMI and weight gain during pregnancy were based on the criteria of the Ministry of Health, Labor and Welfare, and the criteria of the Japan Society for the Study of Obesity. HPD and GDM were diagnosed according to the criteria of the Japan Society of Obstetrics and Gynecology. In this study, preterm birth was defined as birth before 37-week gestational age, and low birth weight was defined as being less than 2500g at birth.

Depressive symptoms

Depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a reliable 10-item questionnaire that has been used to measure depressive symptoms in the prenatal and postnatal periods (Cox et al., 1987; Murray and Cox, 1990; Bennet et.al, 2004). The response to each question ranged from 0 to 3, and the total score ranged from 0 to 30. It was reported that the sensitivity and specificity were 75% and 93%, respectively, in the Japanese version of the EPDS using a cutoff point of 8/9 (Okano et al., 1996). This cut-off point has been commonly used in Japanese prenatal and postnatal studies (Ohara et al., 2018; Takehara et al., 2018; Nakamura et al., 2020). In this study, the Cronbach's α of EPDS was 0.753 in the 2nd trimester and 0.795 in the 3rd trimester.

Anxiety

Anxiety was measured using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1971). The STAI is composed of state anxiety and trait anxiety. State anxiety indicates temporary anxiety at the time of assessment. Trait anxiety indicates

more general and long-term anxiety. Both scales consist of 20 items rated on a 4-point Likert scale ranging from 1 to 4. The scores range from 20 to 80, with higher scores indicating stronger anxiety. The Japanese version of the STAI reported high reliability and validity (Nakazato et al., 1982). For women, the cutoff scores of state anxiety 41/42 and trait anxiety 44/45 were adopted for the assessment of anxiety in previous Japanese studies (Yamanishi et al., 2013; Koyama et al., 2016). The Cronbach α of state anxiety was 0.915-0.917, and trait anxiety was 0.911-0.920, in this study.

Plasma cortisol

Maternal blood samples were collected as part of a routine blood test in the second trimester and transported to the laboratory within a day (Japan Clinical Laboratories, Inc. Kyoto Japan). The cortisol level was assayed by an electrochemiluminescence immunoassay (ECLIA) in the laboratory. Intra-assay and inter-assay coefficients variation were <20% and <15%, respectively.

Saliva oxytocin

Maternal saliva samples were collected using a saliva collection aid (SCA) (Salimetrics, LLC, Carlsbad, CA) in a private outpatient room after a routine check-up. Participants were asked not to eat or drink for 30-60 minutes before sample collection. SCAs and cryovials were kept ice-chilled for collection. At least 1.0 mL of saliva was collected by passive drool. All participants' saliva samples were collected after a routine checkup in the same room. After collection, saliva samples were transported and stored at -80°C in the researcher's laboratory. According to previous research, saliva samples were extracted to concentrate by four times (Carter et al., 2007). The oxytocin level was assayed in duplicates using commercial enzyme-linked immunosorbent assay (ELISA) kits (ENZO Life Sciences, Ann Arbor, MI.), following the product manual (Product Manual Oxytocin ELISA kit). The product manual reported that the intra-assay and inter-assay coefficients of variability were 12.6-13.3% and 11.9-20.9%, respectively. The intra-assay coefficient variation in this study was $\leq 19.8\%$.

Ethics approvals

This study was reviewed and approved by Osaka University Research Ethics Committee (16464). All participants gave written informed consent.

Statistical analysis

Descriptive statistics were used to identify maternal and pregnancy characteristics. To address the issue of missing data of the third trimester, the last observation carried forward was conducted in two cases. The log-transformation was performed for plasma cortisol and salivary oxytocin levels (common logarithm). Normal distributions of continuous variables were confirmed using the Shapiro-Wilk test. An independent *t*-test or Mann-Whitney *U* test was conducted to compare continuous variables between groups. Pearson's product-moment correlation coefficient or Spearman's rank correlation coefficient was calculated to examine the relationship between the continuous variables.

Hierarchical multiple linear regressions were conducted to examine the relationship between the independent variables and infant birth weight. The models were adjusted for the potential confounding variables based on previous studies (Nordeng et al, 2012; Ibanez et al., 2012; Chang et al., 2014; Yang et al., 2017): maternal age, education, and pre-pregnancy BMI. Categorical variables were coded as dummy

variables. Stepwise variable selection was used in the models. First, we set the pregnancy characteristics variables as independent variables in model 1. These variables also refer to previous studies. Then, we added the prenatal mental health variables to model 1 (model 2). Multicollinearity was examined by the correlation matrix of the independent variables and the variance inflation factor (VIF). We confirmed the normal distribution of residuals using a normal probability plot. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS version 24.0 (IBM Corp. Armonk, NY).

RESULTS

Participant characteristics

A total of 81 primiparas participated in the study. There was no difference in age, education, marital status, family form, household income, and pre-pregnancy BMI between participants and dropouts. The questionnaires were given at 24.1 ± 1.8 weeks in the second trimester, and at 36.5 ± 0.6 weeks in the third trimester, blood collection for cortisol was 26.3 ± 1.3 weeks, and saliva collection for oxytocin was 22.9 ± 1.7 weeks.

Table 1 summarizes the maternal demographic and pregnancy characteristics of participants. The mean maternal age was 32.4 ± 3.9 years, 50.6% were university graduates and 96.3% were married. In total, 56.8 % of infants were born by spontaneous vaginal delivery, 61.7% were male, median gestational age was 39.5 (38.6, 40.3) weeks, and the mean birth weight was 3015.7 ± 357.3 g. Four infants (4.9%) were born prematurely, and six infants (7.4%) had low birth weight.

Table 1. Maternal demographic and pregnancy characteristics

		N = 81
		N (%) / Mean \pm SD / Median (IQR)
Age (year)		32.4 \pm 3.9
Education	Secondary or High school	11 (13.6)
	Junior or Technical college	25 (30.9)
	University	41 (50.6)
	Graduate school	4 (4.9)
Marital status	Married	78 (96.3)
	Single	3 (3.7)
Family form	Nuclear family	78 (96.3)
	Extended family	3 (3.7)
Household income/year (JPY)	< 2 million	2 (2.5)
	2-5.9 million	47 (58.0)
	\geq 6 million	32 (39.5)
Employed during pregnancy	Yes	53 (65.4)
History of miscarriage	Yes	19 (23.5)
Infertility treatment	Yes	23 (28.4)
Smoking during pregnancy	Yes	1 (1.2)
Alcohol during pregnancy	Yes	2 (2.5)
Pre-pregnancy BMI [†]	Underweight (<18.5)	7 (8.6)
	Normal weight (18.5-24.5)	67 (82.7)
	Overweight (25.0-29.9)	7 (8.6)
Weight gain during pregnancy [†]	Below	13 (16.0)
	Within	38 (46.9)
	Adobe	30 (37.0)
HPD	Yes	5 (6.2)

GDM	Yes	2 (2.5)
Mode of delivery	Spontaneous vaginal delivery	46 (56.8)
	Vaginal delivery with epidural	11 (13.6)
	Emergency C-section	3 (3.7)
	Scheduled C-section	21 (25.9)
Infant sex	Male	50 (61.7)
	Female	31 (38.3)
Gestational age (week)		39.5 (38.6, 40.3)
Infant birth weight (g)		3015.7 ± 357.3

Abbreviation: BMI = Body mass index, HDP = Hypertensive disorders of pregnancy, GDM = Gestational diabetes mellitus.

† Based on the criteria of the Ministry of Health, Labor and Welfare, and the criteria of the Japan society for the study of obesity.

Maternal prenatal depressive symptoms, state anxiety, trait anxiety, and infant birth weight

Table 2 shows the results of infant birth weight by maternal prenatal depressive symptoms, state anxiety, and trait anxiety. EPDS ≥ 9 was 19.8 % in the second trimester and 16.0% in the third trimester. STAI-S ≥ 42 , STAI-T ≥ 45 were 29.6% and 23.5%, respectively, in the second trimester, and 27.2% in the third trimester. In the second trimester, there was no significant difference between maternal depressive symptoms, state anxiety, trait anxiety, and infant birth weight. In the third trimester, the birth weight of infants of non-depressed women was significantly higher than that of depressed women ($t=2.93$, $df=79$, $p=0.004$). Similarly, the infant's birth weight of non-anxious women was significantly higher than that of anxious women (state anxiety and trait anxiety: $t=2.04$, $df=79$, $p=0.044$; $t=2.33$, $df=79$, $p=0.022$, respectively).

Table 2. Infant birth weight according to maternal EPDS, state anxiety, and trait anxiety scores

						N = 81
			Infant birth weight (g)			
			N (%)	Mean \pm SD	<i>t</i>	<i>p</i>
Second trimester	EPDS	< 8	65 (80.2)	3026.8 \pm 359.9	0.56	0.576
		≥ 9	16 (19.8)	2970.6 \pm 354.6		
	State Anxiety	< 41	57 (70.4)	3060.8 \pm 318.8	1.89	0.062
		≥ 42	24 (29.6)	2894.7 \pm 429.8		
	Trait Anxiety	< 44	62 (76.5)	3043.6 \pm 345.8	1.27	0.207
		≥ 45	19 (23.5)	2924.7 \pm 388.4		
Third trimester	EPDS	< 8	68 (84.0)	3064.3 \pm 338.5	2.93	0.004
		≥ 9	13 (16.0)	2761.4 \pm 357.6		
	State Anxiety	< 41	59 (72.8)	3067.3 \pm 339.7	2.04	0.044
		≥ 42	22 (27.2)	2839.1 \pm 375.2		
	Trait Anxiety	< 44	59 (72.8)	3070.8 \pm 334.4	2.33	0.022
		≥ 45	22 (27.2)	2868.0 \pm 382.3		

Note: Unpaired *t*-test

Table 3. Correlation between plasma cortisol level, salivary oxytocin level and infant birthweight

		N = 81	
	Mean \pm SD / Median (IQR)	Infant birth weight	
Plasma cortisol level ($\mu\text{g/dL}$)	20.6 \pm 5.9	<i>r</i>	0.047
		<i>p</i>	0.679
Salivary oxytocin level (pg/mL)	28.8 (19.1, 96.7)	<i>rs</i>	0.075
		<i>p</i>	0.507

Note: *r* = Pearson's product-moment correlation coefficient, *rs* = Spearman's rank correlation coefficient

Table 4. Maternal plasma cortisol and salivary oxytocin levels according to EPDS, state anxiety, and trait anxiety scores

			Plasma cortisol level ($\mu\text{g/dL}$)		Salivary oxytocin level (pg/mL)	
			Median (IQR)	<i>p</i>	Median (IQR)	<i>p</i>
Second trimester	EPDS	< 8	20.0 (16.4, 23.5)	0.849	27.5 (19.1, 57.8)	0.229
		≥ 9	19.4 (18.1, 25.1)		56.7 (22.6, 114.8)	
	State Anxiety	< 41	20.0 (16.8, 23.7)	0.975	28.6 (18.9, 94.7)	0.745
		≥ 42	19.8 (16.4, 23.6)		30.4 (20.5, 91.0)	
	Trait Anxiety	< 44	20.2 (16.3, 24.0)	0.672	28.2 (18.7, 115.0)	0.996
		≥ 45	19.4 (16.8, 21.0)		29.3 (22.8, 56.5)	
	EPDS	< 8	20.2 (16.4, 24.7)	0.312	29.6 (18.9, 108.2)	0.757
		≥ 9	18.8 (16.9, 20.9)		25.7 (21.7, 30.9)	
Third trimester	State Anxiety	< 41	20.3 (17.3, 24.0)	0.242	31.2 (18.7, 102.3)	0.694
		≥ 42	19.0 (16.3, 21.4)		25.8 (20.7, 69.6)	
	Trait Anxiety	< 44	20.3 (16.9, 23.7)	0.504	29.6 (19.1, 114.8)	0.402
		≥ 45	19.0 (16.4, 22.0)		26.7 (20.0, 32.6)	

Note: Mann-Whitney *U* test

Maternal prenatal cortisol, oxytocin, and infant birth weight

Plasma cortisol levels and salivary oxytocin levels in the second trimester are presented in Table 3. The mean cortisol level was 20.6 \pm 5.9 $\mu\text{g/dL}$ (range 9.5-42.7 $\mu\text{g/dL}$), and the median oxytocin level was 28.8 (19.1, 96.7) pg/mL (range, 9.0-275.0 pg/mL). Table 3 shows the results of the correlation. There was no significant correlation between plasma cortisol, saliva oxytocin, and infant birth weight.

Maternal prenatal depressive symptoms, state anxiety, trait anxiety, cortisol, and oxytocin

Table 4 shows the results of maternal plasma cortisol level and salivary oxytocin level according to depressive symptoms, state anxiety, and trait anxiety. There was no significant difference in plasma cortisol levels and salivary oxytocin levels.

Table 5. Multivariable beta estimates for associations between maternal characteristics, prenatal mental health, and infant birth weight

	β	B	95% CI		<i>p</i>	R^2	<i>adj. R^2</i>
Model 1						0.348	0.295
Gestational age	0.38	16.26	7.50	25.03	0.000		
HDP	-0.30	-441.18	-725.43	-156.93	0.003		
Weight gain during pregnancy	0.22	22.71	2.06	43.36	0.032		
Model 2						0.418	0.362
Gestational age	0.34	14.45	6.02	22.88	0.001		
HDP	-0.26	-382.56	-655.93	-109.19	0.007		
Weight gain during pregnancy	0.26	26.03	6.25	45.81	0.011		
Depressive symptoms in the third trimester	-0.27	-264.63	-442.92	-96.34	0.004		
Δ Model 2-1						0.070	0.067

Abbreviation: BMI = Body mass index, HDP = Hypertensive disorders of pregnancy.

Note: Models adjusted for age, education, and pre-pregnancy BMI. Stepwise variable selection was used in both models. Model 1, Independent variables were the pregnancy characteristics variables: history of miscarriage, weight gain during pregnancy, HDP, infant sex, and gestational age.

Model 2, Independent variables were the pregnancy characteristics variables, and the prenatal mental health variables: depressive symptoms in the second and the third trimester, state anxiety in the second and the third trimester, trait anxiety in the second and the third trimester, cortisol level and oxytocin level in the second trimester.

Associations between maternal characteristics, prenatal mental health, and infant birth weight

The results of linear regression to examine associations between pregnancy characteristics, prenatal mental health, and infant birth weight are shown in Table 5. In model 1, pregnancy characteristics variables were used as independent variables. By stepwise selection, three variables remained: gestational age, HDP, and weight gain during pregnancy ($R^2=0.348$, *adj. R^2*=0.295). In model 2, depressive symptoms, state anxiety, trait anxiety, cortisol level, and oxytocin level were added to model 1 as prenatal mental health variables. Only depressive symptoms remained in the third trimester ($\beta=-0.27$, $B=-264.63$, $p=0.004$), and R^2 increased from model 1 ($R=0.418$, *adj. R^2* =0.362, $\Delta R^2=0.070$, Δ *adj. R^2*=0.067).

DISCUSSION

In this study, depressive symptoms were 19.8 % in the second trimester and 16.0% in the third trimester. State anxiety and trait anxiety were 29.6% and 23.5%, respectively, in the second trimester, and 27.2% in the third trimester. The prevalence of depressive symptoms was similar to previous Japanese studies examined by EPDS. Sugishita et al. (2013) reported that the depressive symptoms were 14.4 % in the second trimester and 14.1% in the third trimester. Ishikawa et al. (2011) reported that the prevalence of depressive symptoms was 14.3% in early pregnancy and 11.8% in late pregnancy. In studies in North America, the prevalence was 9.1% in the second trimester and 10.4% in the third trimester (Straub et al., 2012; Bowen et al., 2012). The prevalence of prenatal depressive symptoms seems to be higher in Japan than in North America. Research in Europe showed a prevalence of approximately 13.8% in the second trimester and 14.6% to 17.2% in the third trimester (Rubertsson et al., 2005; Barker et al., 2011; Jairaj et al.,

2019). Moreover, the prevalence was 18.6-36.5% in other East Asian countries (Choi et al., 2014; Tsao et al., 2016; Lau et al., 2018) and 19-36.3% in Middle East countries (Mohammad et al., 2011; Abdollani et al., 2014; Cankourur et al., 2015). Gavin et al. (2011) have reported racial differences in prenatal depressive symptoms. The prevalence of depressive symptoms in each trimester may differ according to race or ethnicity. The present study found prenatal anxiety levels to be slightly lower but with a similar incidence as other Japanese studies investigating STAI. Sato (2006) reported that state anxiety was 35.4%, and trait anxiety was 26.5% in the third trimester. In a French study, Ibanez et al. (2012) reported that state anxiety was 7.9% in the second trimester. Prenatal anxiety in Japanese women is likely to be higher than that in French women.

Bivariate correlation analysis showed that plasma cortisol levels were not related to infant birth weight. Whereas several studies have investigated the association between maternal cortisol and preterm birth (Kramer et al, 2009; Bandoli et al, 2018; Duffy et al., 2018), few studies have focused on infant birth weight. Cho et al. (2017) examined the association between maternal postpartum cortisol levels and health outcomes of very-low-birth weight infants. There was no significant relationship between cortisol level and birth weight. Cho et al. investigated 40 mothers who delivered premature infants. All participants had medical complications at birth, such as premature prolonged rupture of the membranes. Thus, there is a possibility that other factors related to preterm birth influenced the results. Moreover, Bandoli et al. (2018) have reported the association between cortisol in second trimester and preterm birth, among non-Hispanic white mothers. However, there were no significant results among any other races. These relationships might be differ by races. It is difficult to conclude that maternal cortisol is not related to infant birth weight because only a few studies have been conducted. Future research needs to examine if there is such association for each trimester.

Maternal depressive symptoms were related to lower infant birth weight, but saliva oxytocin was not. Zelkowitz et al. (2014) reported that maternal plasma oxytocin of the third trimester is related to depressive symptoms. The present study found no significant relationship between saliva oxytocin in the second trimester and depressive symptoms. The association might differ depending on the trimester or type of sample, such as saliva or blood samples. It has also been reported that plasma oxytocin levels are related to a variety of conditions (MacDonald and MacDonald, 2010). This needs further research that is controlled by the timing and the environment of sample collection.

Multiple linear regression showed that maternal depressive symptoms in the third trimester predicted lower infant birth weight. This result supports Malaysian and Bangladeshi research (Nasreen et al.; 2010, Nasreen et al.; 2019). In both studies, Nasreen et al. found a significant association between the EPDS score of the third trimester and low birth weight. Meanwhile, maternal depressive symptoms in the second trimester did not predict lower infant birth weight in present study. Accortt et al. (2018) showed that depressive symptoms in early pregnancy did not associate with adverse perinatal outcome, such as low birth weight, preterm birth, small for gestational age. Maternal depressive symptoms may affect infant birth weight in late pregnancy rather than early pregnancy. In general, other maternal factors related to low birth weight are known, such as poor gestational weight gain, hypertensive disorders of pregnancy, short interpregnancy intervals (Hobel and Culhane, 2003; Imdad and Bhutta, 2013). Not only prevention of these factors, but also mental health care for depressive symptoms in late pregnancy might be important for infant birth weight.

In the present study, maternal anxiety in the second trimester, and third trimester did not predict lower infant birth weight. The results of previous studies that examined

anxiety were inconsistent. Liou et al. (2016) investigated the Zung Self-reported Anxiety Scale and found a significant association between anxiety in the third trimester and low birth weight. Similarly, a Bangladeshi study reported that the third trimester's trait anxiety score was related to low birth weight (Nasreen et al., 2010). Nevertheless, Nasreen et al. (2019) using the Depression Anxiety and Stress Scale, reported that prenatal anxiety was not related to low birth weight. Other studies that used a unique questionnaire also found no significant association (Yang et al., 2017; Dowse et al, 2020). Previous studies have used various indicators of anxiety; therefore, further research is needed using a uniform scale.

This study has some limitations. First, because 81 primiparas participated from one research hospital, the generalizability of the research is limited. Moreover, we invited only primiparas for this study. Second, although we limited the environment of saliva and blood collection, we could not limit the timing sufficiently. Diurnal rhythms of cortisol and oxytocin have been reported (Eriksson et al., 1989; Lindow et al., 1996). In addition, these biomarkers were collected only once in the second trimester. For more accurate surveys, multiple collections within a limited time are needed.

CONCLUSION

In conclusion, maternal depressive symptoms in the third trimester predicted lower infant birth weight. Nevertheless, depressive symptoms in the second trimester and anxiety in the second and third trimester did not predict infant birth weight. Similarly, maternal plasma cortisol levels and salivary oxytocin levels in the second trimester were not related to infant birth weight. Maternal mental health care for depressive symptoms in late pregnancy might be important for infant birth weight increases.

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