Associations of Hormonal Biomarkers With Mental Health and Healthy Behaviors Among Mothers of Very-Low-Birthweight Infants

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Abstract

Objectives: To examine the concurrent use of self-report questionnaires and hormonal biomarkers, specifically levels of testosterone and cortisol, along with demographic variables and corrected age (CA) in the assessment of mental health and healthy behaviors among mothers of very-low-birthweight (VLBW, BW < 1,500 g) infants at five time points over 2 years post birth. **Method:** Data on 40 mothers from a neonatal intensive care unit of a tertiary medical center in the southeast United States were collected from the medical record, standard questionnaires for the mother (depressive symptoms, perceived stress, anxiety, mental health status, parenting stress, and healthy lifestyle behaviors), and biochemical measurement of maternal testosterone and cortisol using enzyme immunoassay at birth, 40 weeks' postmenstrual age, and 6, 12, and 24 months CA. **Results:** Maternal self-report of mental health improved from birth to 6 or 12 months then worsened at 24 months. Mixed linear models showed that mothers with higher testosterone levels had more depressive symptoms and smoked more, whereas mothers with higher cortisol levels had healthier behaviors and exercised more. Testosterone levels were negatively correlated with cortisol levels. Marital status, education, and health insurance were the most predictive demographic variables for the levels of hormonal biomarkers, mental health, and healthy behaviors. **Conclusions:** The use of self-report and biochemical measurement was effective in assessing maternal mental health and healthy behaviors over 2 years post birth, when mothers of VLBW infants tend to experience more mental health problems and parenting difficulties than mothers of normal-BW full-term infants.

Keywords

hormonal biomarkers, maternal mental health, maternal healthy behaviors

Maternal mental health is important not only for maternal well-being but also for infant health and development (Brockington, Butterworth, & Glangeaud-Freudenthal, 2017). However, about 13–19% of mothers experience psychological problems during the postpartum period, including 18% with elevated postpartum anxiety symptoms and 19–35% with elevated depressive symptoms that adversely affect maternal health and infant development (O'Hara & McCabe, 2013). Postpartum mental health problems usually occur within 4 weeks of birth, and the first 6 months post birth is a particularly difficult time for mothers with these problems. Also, mothers of infants with negative birth outcomes such as being very preterm (gestational age < 32 weeks) and very-low-birthweight (VLBW, BW < 1,500 g) have reported more problematic mental health than mothers of normal-BW full-term infants (Staehelin, Kurth, Schindler, Schmid, & Zemp Stutz, 2013). These infants require intensive involvement from their mothers and health-care providers to survive, and mothers worry about their health outcomes (Holditch-Davis, Schwartz, Black, & Scher, 2007; Howe, Sheu, Wang, & Hsu, 2014). This extra parenting burden that mothers of VLBW preterm infants face likely plays an important role in the increase in mental health problems these

mothers report relative to other mothers (J. Cho, Holditch-Davis, & Miles, 2008; Howe et al., 2014; Witt et al., 2012).

Mothers of VLBW infants usually report more depressive symptoms and greater symptoms of anxiety than other mothers, especially during their infant's hospitalization in the neonatal intensive care unit (NICU). Mental health problems among these mothers decrease after the infant's discharge from the NICU. However, researchers have found that mental health problems, including parenting stress, increase more over the first years of life among mothers of VLBW infants than among mothers of full-term infants (J. Cho, Su, Phillips, & Holditch-Davis, 2016; Howe et al., 2014).

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Researchers and health-care providers have generally assessed mental health using self-report questionnaires, which may over- or underestimate the problems because of elevated social desirability that obscures their frequency and severity (Gao et al., 2015; Lau, Hurst, Smith, & Schanler, 2007). One possible way to improve the accuracy of self-report questionnaires would be to combine their use with other measures such as assessment of biochemical markers. Use of self-report questionnaires in combination with hormonal biomarkers, such as testosterone and cortisol, might provide more effective risk identification than do self-report questionnaires alone.

Cortisol is a key hormone for activation of the stress response and, thus, has been widely used as a biomarker to assess psychological disorders (Lancaster et al., 2010). Cortisol levels normally increase significantly during pregnancy, peak at delivery, and decline to baseline levels within the first 3 days postpartum. The elevated levels of cortisol during pregnancy, which are due to the production of placental corticotrophin-releasing hormone, increase susceptibility to mental health problems, and the degree of elevation is associated with negative pregnancy outcomes such as short gestation and low BW (Bolten et al., 2011; Owen, Wood, Tomenson, Creed, & Neilson, 2017). Cortisol levels are expected to return to prepregnancy baseline levels during the postpartum period through self-adjustment. However, an overadjustment can lead to hypocortisolemia and trigger mental health problems such as depressive symptoms (Seth, Lewis, & Galbally, 2016). A systematic literature review that included 47 studies showed that hypercortisolemia during the antenatal and immediate postpartum (1–6 days) periods is linked to transient depressive states, whereas hypocortisolemia at 4–6 weeks postpartum and within 12 months postpartum is related to chronic postpartum depression (Seth et al., 2016).

Similarly, investigators have attempted to correlate testosterone levels with maternal mental health problems. However, the direction of the association has been inconsistent across study findings. Researchers have found that either very low or very high testosterone levels are related to women's well-being and depression postpartum, such that low androgen levels are associated with low self-esteem, decreased feelings of well-being, and depression, whereas high levels are associated with inconsistent behavior and depression (Blehar, 2006; Rohr, 2002). In one study, mothers with low testosterone levels reported more depressive symptoms and were more often diagnosed with depressive and anxiety disorders, social phobia, and agoraphobia than mothers with normal testosterone levels (Giltay et al., 2012). In addition, the results from a study among a sample of adults of reproductive age that was representative of the U.S. population showed that married or partnered mothers had lower testosterone levels and a lower prevalence of depression than unmarried mothers or partnered nonmothers (Gettler & Oka, 2016). Meanwhile, other researchers found that high testosterone levels were related to mental health problems including depression, mood disturbances, baby blues, and anger across the pre- and postpartum periods, especially among mothers with low socioeconomic status (Buckwalter et al.,

1999; Gettler & Oka, 2016; Hohlagschwandtner, Husslein, Klier, & Ulm, 2001). Buckwalter et al. (1999) found that, during the postpartum period, maternal testosterone levels were positively associated with mood disturbances and depression, but other hormones, such as progesterone and dehydroepiandrosterone, attenuated those associations. Health-related factors such as cigarette smoking and body mass index (BMI) accounted for the high prevalence of depression and depressive symptoms among unmarried mothers.

Research has shown that the perinatal levels of cortisol and testosterone are correlated in women during the perinatal period (J. I. Cho, Carlo, Su, & McCormick, 2012; Sarkar, Bergman, Fisk, O'Connor, & Glover, 2007). Thus, we decided to measure both cortisol and testosterone levels longitudinally over 2 years post birth to assess their utility in identifying maternal mental health problems in combination with the self-report questionnaires. Although findings regarding an association between testosterone levels and women's mental health have varied, we hypothesized that the analysis of testosterone and cortisol levels combined with self-report would provide more precise information than self-report alone for assessment of maternal mental health problems.

Because health-related factors such as cigarette smoking are related to maternal mental health (Räsänen et al., 2014), we also examined healthy lifestyle behaviors (which we will refer to throughout as healthy behaviors) among mothers of VLBW infants to confirm the direction of the results of the combined self-report and biochemical measurement. Healthy behaviors (healthy eating, physical activity, no cigarette smoking, and no use of alcohol) are protective factors for mental health problems (Kowalska, Olszowa, Markowska, Teplik, & Rymaszewska, 2014; Räsänen et al., 2014; Vilela et al., 2015). Health-care providers encourage healthy behaviors in pregnant women to improve nutritional status, prevent excessive weight gain, and ameliorate medical complications such as diabetes and hypertension (Bogaerts et al., 2013; McGivern et al., 2015). For postpartum women, providers encourage healthy behaviors to reduce retention of pregnancy weight gain because obesity is often associated with poor mental health (Marchi, Berg, Dencker, Olander, & Begley, 2015). Research has shown physical activity to be effective in reducing the risks of anxiety, phobias, panic attacks, stress disorders, depressive symptoms, and postpartum depression (Janisse, Nedd, Escamilla, & Nies, 2004; Penedo & Dahn, 2005; Richardson et al., 2005). When the effects of healthy behaviors have been assessed using self-report alone, the predictive outcomes have been inconsistent. Thus, combining the measures of self-report with biochemical markers is likely to improve these outcomes.

The purpose of this study was to examine the concurrent use of self-report and biochemical measures along with demographic variables and corrected age (CA) in the assessment of maternal mental health and healthy behaviors during the 2 years after birth. We hypothesized that the maternal hormonal biomarkers of testosterone and cortisol levels would predict mental health and healthy behaviors. To test our hypothesis (see Figure 1), we examined whether self-reported maternal

Figure 1. Conceptual framework for associations among hormonal biomarkers, mental health, healthy behaviors, and demographic characteristics among mothers of very-low-birthweight infants.

mental health and healthy behaviors were associated with the levels of testosterone and cortisol longitudinally at five time points (at birth, 40 weeks postmenstrual age [PMA], and 6, 12, and 24 months infant CA). We also examined whether maternal healthy behaviors were associated with mental health across four time points (40 weeks PMA and 6, 12, and 24 months infant CA). Finally, we examined whether maternal demographic characteristics such as marital status and BMI were associated with the levels of hormonal biomarkers, mental health, or healthy behaviors longitudinally.

Method

We used a descriptive research design for this exploratory study and collected data through review of infants' medical records, interviews with mothers, biochemical measurement, and standardized questionnaires.

Participants

We recruited a convenience sample of 40 mothers of VLBW infants from the NICU of a tertiary medical center in the southeastern United States. Mothers were eligible if they (a) had given birth 3 days prior to recruitment (to avoid recruiting mothers whose infants died shortly after birth), (b) were older than 15 years (to avoid recruiting mothers who were too young to thoroughly understand consent), (c) spoke English, and (d) were a primary caregiver of the infant. To reduce potential confounding effects, we excluded mothers who (a) were dependent on narcotics or other drugs, (b) were HIV positive, or (c) had a documented serious medical problem such as cancer or psychosis.

Measures

The maternal data we collected included demographic information, pregnancy history and birth record, mental and physical health, healthy behaviors, and hormonal biomarkers. We collected demographic information, pregnancy history, and birth record from the infant's medical record. Similar to mental

health, we measured physical health at four time points (at 40 weeks PMA and 6, 12, and 24 months infant CA) using the 12-item short-form survey (SF-12), which consists of a mental health composite score (SFMCS) and a physical health composite score (SFPCS).

Maternal mental health. We assessed maternal mental health longitudinally at three to five time points, depending on the measure (birth; 40 weeks PMA; and 6, 12, and 24 months infant CA). Specifically, we collected data for depressive symptoms, anxiety, and perceived stress at all five time points, asked mothers to complete the mental health survey at all time points except for at birth because mothers had to be home to report their ability to complete domestic chores, and collected data on parenting stress at three time points (6, 12, and 24 months infant CA), as we wanted mothers to have parenting experiences with the infant at home before we collected this variable.

Depressive symptoms. We used the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) to assess maternal depressive symptoms during the postpartum period. Scores range from 0 to 60, with higher scores indicating more depressive symptoms. Internal consistency using Cronbach's α was reported as .85 to .90. The internal consistency of the CES-D in the present study ranged from .86 to .90 across the five time points.

Anxiety. To assess maternal anxiety, we used the 6-item short form of the state scale in the Spielberger State-Trait Anxiety Inventory (STAI/SF; Marteau & Bekker, 1992). Scores range from 0 to 6, with higher scores indicating more anxiety. Internal consistency using Cronbach's α was reported as .83 (van der Bij, de Weerd, Cikot, Steegers, & Braspenning, 2003). The internal consistency of the STAI/SF in the present study ranged from .79 to .90 across the five time points.

Perceived stress. We used the 10-item version of Cohen's Perceived Stress Scale (PSS-10; Andreou et al., 2011) to assess maternal perceived stress. Scores range from 0 to 10, with higher scores indicating more perceived stress. Internal consistency using Cronbach's α was reported as .73 to .84 (Andreou et al., 2011; Lesage, Berjot, & Deschamps, 2012). The internal consistency of the PSS in the present study ranged from .82 to .87 across the five time points.

Parenting stress. To measure stress within the parent–infant relationship, we used the 36-item Parenting Stress Index–Short Form (PSI-4/SF; Abidin, 2012). Scores range from 36 to 180, with total scores higher than 90 considered indicators of potential problems in the well-being of the parent and the infant. Internal consistency using Cronbach's α was reported as .78 to .91.

Mental health status. We used the 12-item short-form health survey (SF-12; Ware, Kosinski, & Keller, 1996) to collect data on maternal mental and physical health status. The SF-12

consists of mental (SFMCS) and physical (SFPCS) health composite scores that range from 0 to 100, with higher scores indicating better health. Internal consistency using Cronbach's α was reported as .76 to .89 (King, Horowitz, Kassam, Yonas, & Roberts, 2005; Ware et al., 1996). We used the SFMCS to assess maternal mental health status.

Healthy lifestyle behaviors. We assessed maternal healthy behaviors at four time points (40 weeks PMA and 6, 12, and 24 months CA) as mothers had to be home to report their daily healthy behaviors. We used a questionnaire modified from the Lifestyle Index Questionnaire (LIQ; Kim, Popkin, Siega-Riz, Haines, & Arab, 2004) to assess the behaviors of healthy eating, physical activity, previous and current cigarette smoking, and use of alcohol. Healthy eating was scored based on the frequency at which the mother ate portions from each of the five food groups regularly (meat = 1–3 days/week, dairy = 1–3 days/week, grain = 1–3 days/week, fruits = 1–3 days/week, and vegetable = 1–3 days/week). The total score for healthy eating ranged from 5 (did not eat from all five food groups regularly) to 25 (regular consumption of all food groups), with a higher score indicating that the mother ate from all of the five groups of food more regularly per week. Weekly physical activity was scored for all types of physical activity, with an indication for intensity (*strenuous* = 3, *moderate* = 2, and *mild* = 1). The total score for weekly physical activity ranged from 5 (*no activity*) to 52 (*regular activity*), with a higher score indicating more strenuous and regular physical activity. Specifically, if a mother performed physical activity at all intensity levels (*strenuous* = 3 points per day performed, *moderate* = 2, and *mild* = 1) throughout the week (7 days), she would receive the maximum score of 52 for physical activity (10 points for regular physical activity and 42 points for each level of intensity times the number of days [$3 \times 7 \text{ days} + 2 \times 7 \text{ days} + 1 \times 7 \text{ days}$]). Current smoking behavior was scored as 10 for no smoking. If a mother currently smoked, her score was 5 minus 0 if she smoked 1–4 cigarettes/day, 1 for 5–9 cigarettes/day (1), 3 for 10–19 cigarettes/day, and 5 for more ≥ 20 cigarettes/day. Score for current smoking behavior thus ranged from 0 to 10, with a higher score indicating healthier behavior. Previous smoking behavior was scored as 5 = *yes* or 10 = *no*. As with current smoking, current alcohol usage was scored as 10 for no usage. If a mother currently drank alcohol, her score was 5 minus 0 if she had 5–6 drinks/week, 1 if she had 7–13 drinks/week, 3 if she had 14–27 drinks/week, and 5 if she had ≥ 28 drinks/week. Total score for current alcohol consumption thus ranged from 0 to 10, with a higher score indicating healthier behavior. The overall total score of the LIQ ranged from 15 to 107, with higher scores indicated more healthy lifestyle behaviors. Internal consistency of the LIQ in the present study ranged from .75 to .77 at the four time points.

Saliva sample collection and analysis. We obtained saliva by asking mothers to expectorate through a straw into a small tube 1 hr before or after any oral intake of food or liquid. We collected three saliva samples of 0.1 mL from each mother within a 2-hr

period with at least 15 min between each collection to minimize the effects of the pulsatile and diurnal secretion pattern of hormonal markers (Rosner, Auchus, Azziz, Sluss, & Raff, 2007). We did not use collection devices such as mouth swabs or cotton rolls for saliva collection because they can introduce assay artifacts. All saliva samples were placed on ice to transfer to the laboratory at the university and stored in a -80°C freezer until assay.

A lab technician blinded to maternal demographic information measured maternal salivary testosterone and cortisol levels using an enzyme immunoassay (EIA) at the university laboratory. All samples were measured twice for quality control at each time point (birth, 40 weeks PMA, and 6, 12, and 24 months CA). Maternal saliva samples at birth and 40 weeks PMA were collected in the NICU, whereas the samples at 6, 12, and 24 months CA were collected at either the Newborn Follow-Up Clinic or the research project office.

Testosterone. We measured maternal testosterone levels in saliva because saliva contains free steroids that are unbound to proteins and are more biochemically relevant than those bound to proteins because they are easily accessible to tissues (Rosner et al., 2007). Maternal salivary testosterone levels were determined by EIA following the manufacturer's instructions (Salimetrics, LLC, State College, PA; <https://www.salimetrics.com/assets/documents/1-2402n.pdf>). The intra- and interassay coefficients of variation, which express the precision and repeatability of the assay, were 2.5% and 5.6%, respectively. Testosterone levels are higher in the morning than in the evening (Granger et al., 2003; Papacosta, Gleeson, & Nassiss, 2013). Thus, we collected three samples from each mother between 9 a.m. and noon to reduce the effects of diurnal rhythm on testosterone and to avoid trying to detect extremely low evening testosterone levels.

Cortisol. Cortisol levels vary diurnally and are higher in the morning than in the evening (Mezzullo et al., 2016), so we used the saliva samples collected for testosterone measurement. Salivary cortisol levels were determined by EIA following the manufacturer's instructions (Salimetrics, LLC; <https://www.salimetrics.com/assets/documents/1-3002n.pdf>). The intra- and interassay coefficients of variation were 3.3% and 3.7%, respectively.

Procedure

The institutional review board at the university approved this study. On a daily basis, a research nurse identified eligible mothers for the study through the NICU admission log. The research nurse discussed the study with the mothers and gave them the informed consent form to review. After receiving maternal consent, a research nurse reviewed the mothers' medical information in the infants' medical records and interviewed mothers to complete the data forms (including contact information, demographic information, etc.) at the NICU. At two time points (after birth and at 40 weeks PMA), the research nurse collected maternal saliva samples and asked mothers to

complete the CES-D, STAI/SF, and PSS-10. At 40 weeks PMA, the research nurse and the research assistant updated maternal demographic and contact information for the follow-up visit.

We asked mothers to visit either the Newborn Follow-Up Clinic or the research project office when the infants were 6, 12, and 24 months CA. At each visit, we would schedule the next visit for a time between 9 a.m. and 12 p.m. A month before each visit we would send a reminder to mothers via regular mail and follow up 1 week before the appointment with a phone call and/or text message. During the visits, the research nurse and the research assistant collected saliva samples over a period of 2 hr, as described above, and updated the demographic information of mother. The research nurse also asked mothers to complete the CES-D, STAI/SF, PSS-10, SF-12 (SFMCS), and PSI-4/SF to assess maternal mental health status; to complete the SF-12 (SFPCS) to assess maternal physical health status; and to complete the LIQ to assess maternal healthy behaviors.

Data Analysis

We use descriptive statistics to present maternal demographic characteristics. Linear mixed models were the main analytic tool for determining whether maternal salivary testosterone and cortisol levels were associated with maternal mental health and healthy behaviors longitudinally, while we used Pearson correlations to examine the relationships between the levels of testosterone and cortisol.

Results

Maternal Sociodemographic Characteristics and Hormonal Biomarkers

Of the 40 participating mothers, 45% had more than a high school education, 30% were married, 60% were African American, 70% had a cesarean section, and 40% had private health insurance. Mean maternal age was 26 years, and 95% of the mothers had completed a prenatal glucocorticoid treatment (see Table 1). Means of gravida and parity were 2.5 and 1.9, respectively, and mean BMI was 34.3 kg/m² at admission to the Obstetrics and Gynecological Unit before delivery. A large majority (83%) of the mothers had medical complications during pregnancy such as chorioamnionitis and antepartum hemorrhage, and 100% of the mothers had medical complications at birth such as premature prolonged rupture of the membranes and consequent antibiotic use. As shown in Table 1, the mean maternal testosterone levels at the five time points (birth, 40 weeks PMA, and 6, 12, and 24 months CA) ranged from 52.7 to 64.3 pg/ml, and the mean maternal cortisol levels at the five time points ranged from 0.13 to 0.29 µg/dl.

As shown in Table 2, the mean scores of maternal depressive symptoms and anxiety were highest immediately after birth, decreased from birth to between 6 and 12 months, and then increased at 24 months. The mean mental health status, as indicated by score on the SF-12 (SFMCS), was lowest around

Table 1. Maternal Sociodemographic Characteristics and Hormonal Biomarkers.

Variable	Minimum	Maximum	M (SD)
Age (years)	18	38	25.9 (5.8)
Gravida	1	6	2.5 (1.4)
Parity	1	5	1.9 (1.1)
BMI	20.9	49.4	34.3 (6.9)
Pregnancy complications	0	3	1.1 (0.7)
Complications during labor	2	5	4.4 (0.8)
Maternal testosterone (pg/ml)			
Birth	12.6	158.6	64.3 (34.3)
40 weeks PMA (n = 39)	25.0	110.1	52.7 (18.9)
6 months CA (n = 34)	27.0	134.9	62.6 (23.2)
12 months CA (n = 34)	23.4	128.6	55.5 (22.0)
24 months CA (n = 28)	24.2	111.0	55.7 (23.1)
Maternal cortisol (µg/dl)			
Birth (n = 38)	0.0	0.6	0.1 (0.1)
40 weeks PMA (n = 39)	0.0	0.6	0.2 (0.1)
6 months CA (n = 34)	0.1	1.5	0.3 (0.2)
12 months CA (n = 34)	0.0	0.3	0.2 (0.1)
24 months CA (n = 28)	0.1	0.5	0.2 (0.1)
		n (%)	
Race			
African American		24 (60.0)	
Caucasian		16 (40.0)	
Marital status			
Married		12 (30.0)	
Single		25 (62.5)	
Widowed		1 (2.5)	
Separated		2 (5.0)	
Education			
<High school		7 (17.5)	
High school graduate		15 (37.5)	
Some college		15 (37.5)	
College graduate		2 (5.0)	
>College graduate		2 (2.5)	
Insurance, public		24 (60.0)	
Prenatal steroids, yes		38 (95.0)	
Delivery, vaginal		12 (30)	

Note. N = 40. BMI = body mass index; CA = corrected age; PMA = postmenstrual age.

12 months and improved at 24 months. The mean parenting stress scores increased from 6 months to 24 months. The mean score for healthy behaviors, indicated by score on the LIQ, was highest at 40 weeks PMA and lowest at 12 months.

Associations of Hormonal Biomarkers With Mental Health and Healthy Behaviors

As shown in Table 3, using linear mixed models, we found that mothers with higher testosterone levels showed more depressive symptoms and currently smoked more cigarettes than mothers with lower testosterone levels. Maternal cortisol levels were not associated with any of the maternal mental health variables. However, mothers with higher cortisol levels had more healthy behaviors, such as physical activity, than mothers with lower cortisol levels.

Table 2. Maternal Mental Health and Healthy Lifestyle Behaviors Over the 2 Years After Birth.

Variable	<i>n</i>	Minimum	Maximum	<i>M</i> (<i>SD</i>)
Depressive symptoms (CES-D)				
Birth	40	2	42	13.7 (10.2)
40 weeks PMA	38	2	43	13.0 (9.7)
6 months CA	32	1	34	12.1 (9.6)
12 months CA	34	2	43	11.9 (9.8)
24 months CA	30	0	40	13.0 (11.2)
Perceived stress (PSS-10)				
Birth	40	0	29	14.4 (7.6)
40 weeks PMA	38	0	31	13.4 (8.0)
6 months CA	32	4	30	13.8 (7.3)
12 months CA	34	0	34	14.8 (6.8)
24 months CA	30	0	31	15.1 (7.3)
Anxiety (STAI/SF)				
Birth	40	6	22	10.5 (4.1)
40 weeks PMA	38	6	22	9.3 (4.1)
6 months CA	32	6	21	9.3 (3.7)
12 months CA	34	6	17	9.7 (3.4)
24 months CA	30	6	18	9.9 (4.0)
Mental health status (SF-12 [SFMCS])				
40 weeks PMA	38	24.7	65.4	49.1 (10.5)
6 months CA	32	24.7	60.7	48.5 (9.5)
12 months CA	34	25.8	62.5	47.9 (9.4)
24 months CA	30	22.1	63.8	49.9 (10.7)
Parenting stress (PSI-4/SF)				
6 months CA	32	36	129	57.3 (19.0)
12 months CA	34	37	103	62.5 (18.0)
24 months CA	30	38	117	67.97 (22.3)
Health behaviors (modified LIQ)				
40 weeks PMA	38	50.0	96.0	69.4 (14.1)
6 months CA	31	42.0	95.0	66.3 (12.4)
12 months CA	34	42.0	95.0	62.6 (14.2)
24 months CA	30	42.0	94.0	67.6 (15.0)

Note. *N* = 40. CA = corrected age; CES-D = Center for Epidemiological Studies Depression Scale; LIQ = Lifestyle Index Questionnaire; PMA = post-menstrual age; PSI-4/SF = Parenting Stress Index–Short Form; PSS-10 = Perceived Stress Scale (10-item version); SF-12 (SFMCS) = 12-item short-form health survey, mental health composite score; STAI/SF = State-Trait Anxiety Index, short form (State subscale only).

The levels of testosterone and cortisol were negatively correlated; for example, testosterone levels at 40 weeks PMA were negatively correlated with cortisol levels at 12 months ($r = -.344, p = .05$), whereas cortisol levels at 40 weeks PMA were negatively correlated with testosterone levels at 24 months ($r = -.490, p = .01$). Testosterone levels at 6 and 12 months ($r = .591, p \leq .001$), 6 and 24 months ($r = .498, p = .01$), and 12 and 24 months ($r = .618, p \leq .001$) were positively correlated with each other. We found no correlation among cortisol levels at the five time points.

Associations Between Maternal Healthy Behaviors and Mental Health

As shown in Table 4, linear mixed model analysis showed a number of associations between maternal healthy behaviors and maternal mental health. Specifically, level of maternal

perceived stress was lower in mothers who consumed less alcohol, level of anxiety was lower in mothers with less previous smoking, and level of parenting stress was lower in mothers who ate healthy foods more regularly.

Associations Between Maternal Demographic Characteristics and Hormonal Biomarkers, Mental Health, and Healthy Behaviors

As shown in Table 5, using mixed linear models, we found that marital status, education, and health insurance were the socio-demographic variables most predictive for levels of hormonal biomarkers, mental health, and healthy behaviors. Unmarried mothers reported more mental health problems including higher levels of depressive symptoms, more perceived stress, more anxiety, more parenting stress, and lower mental health status than married mothers. Mothers with more years of education showed lower levels of depressive symptoms, less perceived stress, less anxiety, and fewer healthy behaviors than mothers with fewer years of education. Mothers who had private health insurance had lower levels of depressive symptoms and parenting stress than mothers who had health insurance through a public assistance program such as Medicaid and WIC. Mothers with more medical complications during pregnancy had fewer healthy behaviors than mothers with fewer medical complications. Caucasian mothers reported higher levels of anxiety than African American mothers. Mothers with higher BMIs reported less parenting stress than mothers with lower BMIs. Mothers who had less education, who were without private health insurance, and who had more medical complications during pregnancy had higher levels of testosterone than other mothers. However, we found no associations between maternal demographic characteristics and cortisol levels.

Discussion

Maternal mental health (i.e., depressive symptoms, perceived stress, anxiety, and parenting stress) as well as healthy lifestyle behaviors (i.e., healthy eating, use of cigarettes, and use of alcohol) were associated with levels of the hormonal biomarkers testosterone and cortisol during the 2 years after birth in mothers of VLBW infants in the present study. A number of previous studies have shown that low testosterone levels are associated with mental health problems in men and possibly women (Blehar, 2006; Gettler & Oka, 2016; Giltay et al., 2012; Rohr, 2002). However, we found in the present study that high testosterone levels were negatively associated with not only maternal mental health but also healthy behaviors such that mothers with high testosterone levels showed more depressive symptoms and smoked more cigarettes compared to mothers with low testosterone levels. Furthermore, though cortisol is considered a stress hormone (Lancaster et al., 2010) and has been associated with mental health, either positively or negatively, in numerous studies (Bolten et al., 2011; Owen et al., 2017; Seth et al., 2016), we found no associations between

Table 3. Associations of Levels of Maternal Hormonal Biomarkers (Testosterone and Cortisol) With Mental Health and Healthy Behaviors Over the 2 Years After Birth Using Linear Mixed Models.

Dependent Variable	Parameter							
	Testosterone				Cortisol			
	β	SE	$t(df)$	p	β	SE	$t(df)$	p
Depressive symptoms (CES-D)	.059	.030	1.971 (172)	.05	4.158	4.722	0.881 (169)	.38
Perceived stress (PSS-10)	.016	.022	0.708 (172)	.48	0.026	3.477	0.007 (169)	.99
Anxiety (STAI/SF)	.013	.012	1.142 (172)	.26	0.783	1.835	0.427 (169)	.67
Mental health status (SF-12 [SFMCS])	-.026	.040	-0.655 (132)	.51	-4.249	5.382	-0.790 (132)	.43
Parenting stress (PSI-4/SF)	.146	.090	1.626 (94)	.11	0.630	11.722	0.054 (94)	.96
Healthy behaviors (LIQ)								
Healthy eating	-.004	.005	-0.671 (124)	.50	-1.208	0.723	-1.671 (124)	.10
Physical activity	.009	.051	0.177 (131)	.86	14.395	6.719	2.142 (131)	.04
Current smoking	-.031	.011	-2.774 (130)	.01	0.330	1.528	0.216 (130)	.83
Previous smoking	-.017	.010	-1.821 (131)	.07	-0.443	1.294	-0.342 (131)	.73
Use of alcohol	.002	.007	0.249 (128)	.80	1.358	0.982	1.383 (128)	.17
Total score	-.042	.057	-0.744 (131)	.46	15.058	7.441	2.024 (131)	.05

Note. CES-D = Center for Epidemiological Studies Depression Scale; LIQ = Lifestyle Index questionnaire; PSI-4/SF = Parenting Stress Index–Short Form; PSS-10 = Perceived Stress Scale (10-item version); SF-12 (SFMCS) = 12-item short-form health survey, mental health composite score; STAI/SF = State-Trait Anxiety Index, short form (State subscale only).

cortisol levels and maternal mental health problems from birth to 24 months. However, mothers with higher cortisol levels did practice healthier behaviors, especially physical activity, than mothers with lower cortisol levels. As we found negative correlations between the levels of testosterone and cortisol across the five time points, testosterone levels could consistently predict maternal mental health and healthy behaviors negatively, whereas cortisol levels could consistently predict maternal healthy behaviors positively during the first years after birth. Also, as we longitudinally examined the associations between the levels of hormonal biomarkers and maternal mental health and healthy behaviors at five time points (birth, 40 weeks PMA, and 6, 12, and 24 months CA), our results should be more predictive than the results from cross-sectional and/or short-term longitudinal studies.

The negative associations we found between testosterone levels and maternal mental health and healthy behaviors were amplified when we considered demographic characteristics because variables that were predictive of maternal mental health and healthy behaviors, such as marital status, education, and type of health insurance, were also associated with testosterone levels. Associations between maternal demographic characteristics and mental health have been widely reported (Räsänen et al., 2014; Stachelin et al., 2013). However, no study has also looked at those associations after adding the levels of testosterone and cortisol to the models. We confirmed that testosterone level has negative relationships with both mental health and healthy behaviors as testosterone levels were higher in mothers who had less education, more medical complications during pregnancy, and public rather than private health insurance. Gettler and Oka (2016) found that testosterone levels were higher in never-married mothers and mothers with low socioeconomic status possibly because high

testosterone levels were also associated with less education, which is a proxy for low socioeconomic status. In the present study, maternal education was negatively associated with depressive symptoms, perceived stress, and anxiety as well as healthy lifestyle behaviors.

Investigators have reported that, during the first 2 years of life, infant age was not a significant predictor of parenting stress in mothers of either preterm or full-term infants (Howe et al., 2014). Our results in the present study were mixed. We found that maternal mental health problems (depressive symptoms, perceived stress, and anxiety) were greatest immediately after birth, though the problems decreased from 6 to 12 months after the infant's discharge from the hospital. But then all mental health problems increased at 24 months, including parenting stress, whereas mental health status measured by the SF-12 was worst at 12 months and best at 24 months, exactly the opposite trajectory compared to the other mental health variables (depressive symptoms, perceived stress, anxiety, and parenting stress).

Healthy behaviors in the present study were negatively associated with mental health problems, such that mothers showed the healthiest behaviors at 40 weeks PMA when they also reported the lowest levels of perceived stress and anxiety. This finding makes sense because healthy behaviors such as healthy eating and physical activity are known to reduce women's mental health problems before and after childbirth (Howard & Khalifeh, 2015; Vilela et al., 2015). We also found that mothers who consumed more alcohol reported higher levels of perceived stress, mothers who smoked more cigarettes showed higher levels of anxiety, and mothers who ate healthy food more regularly showed lower levels of parenting stress across four time points between 40 weeks PMA and 24 months CA. On the other hand, healthy behaviors were not associated

Table 4. Associations Between Maternal Healthy Behaviors and Mental Health Over the 2 Years After Birth Using Linear Mixed Models.

Dependent Variable	Parameter														
	Healthy Eating			Physical Activity			Current Smoking			Previous Smoking			Use of Alcohol		
	β	SE	t(df)	β	SE	t(df)	β	SE	t(df)	β	SE	t(df)	β	SE	t(df)
Depressive symptoms (CES-D)	-0.522	0.644	-0.810 (125)	.42	0.030	0.067	0.449 (133)	.65	0.037	0.304	0.122 (132)	.90	-0.623	0.352	-1.767 (133)
Perceived stress (PSS-10)	-2.207	0.489	-0.423 (125)	.67	-0.084	0.050	-1.703 (133)	.09	-0.016	0.226	-0.073 (132)	.94	-0.462	0.262	-1.759 (133)
Anxiety (STAI/SF)	0.133	0.253	0.528 (125)	.60	-0.002	0.026	-0.080 (133)	.94	-0.112	0.117	-0.958 (132)	.34	-0.427	0.132	-3.232 (133)
Parenting stress (PSI-4/SF)	-5.010	1.287	-3.893 (87)	.00	-0.210	0.164	-1.276 (95)	.20	0.385	0.728	1.147 (94)	.25	-1.006	0.861	-1.169 (95)
Mental health status (SFMCS)	0.132	0.651	0.203 (125)	.84	0.054	0.068	0.796 (133)	.43	-0.051	0.308	-0.165 (132)	.87	0.480	0.359	1.338 (133)

Note. CES-D = Center for Epidemiological Studies Depression Scale; PSI-4/SF = Parenting Stress Index-Short Form; PSS-10 = Perceived Stress Scale (10-item version); STAI/SF = State-Trait Anxiety Index, short form (State subscale only).

Table 5. Significant Associations Between Demographic Characteristics and Hormonal Biomarkers (Testosterone and Cortisol), Mental Health, and Healthy Behaviors Over the 2 Years After Birth Using Linear Mixed Models.

Dependent Variable	Parameter	β	SE	$t(df)$	p
Testosterone	Education	−6.412	1.980	−3.238 (175)	<.001
	Insurance	7.773	3.564	2.181 (175)	.03
	Preg. complication	7.347	2.786	2.637 (175)	.01
Depressive symptoms (CES-D)	Marital status	5.545	0.893	6.208 (174)	<.001
	Education	−1.946	0.978	−2.439 (174)	.02
	Insurance	4.864	1.392	3.493 (174)	<.001
Perceived stress (PSS-10)	Marital status	2.075	0.709	2.925 (174)	<.001
	Education	−1.346	0.589	−2.286 (175)	.02
	Marital status	1.670	0.360	4.634 (174)	<.001
Anxiety (STAI/SF)	Education	−6.412	1.980	−3.238 (175)	<.001
	Race	1.673	0.588	2.845 (175)	.01
	Marital status	−3.897	1.154	−3.378 (125)	<.001
Mental health status (SFMCS)	Marital status	9.649	3.223	2.994 (96)	<.001
Parenting stress (PSI-4/SF)	Insurance	7.721	3.089	2.027 (96)	.05
	Body mass index	−0.821	0.274	−2.992 (96)	<.001
	Education	−2.966	1.272	−2.332 (133)	.02
Healthy behaviors (LIQ)	Education	−2.966	1.272	−2.332 (133)	.02
	Preg. complication	−4.044	1.774	−2.280 (133)	.02

Note. Only significant associations ($p < .05$) are presented. CES-D = Center for Epidemiological Studies Depression Scale; Preg. complication = medical complications during pregnancy; PSI-4/SF = Parenting Stress Index–Short Form; PSS-10 = Perceived Stress Scale (10-item version); STAI/SF = State-Trait Anxiety Index, short form (State subscale only).

with mental health status as measured by the SF-12. These findings suggest that using a combination of self-report and hormonal biomarkers provide a more accurate picture of the nature of maternal mental health problems and healthy behaviors during the first years after birth.

This study had several limitations. We used self-report questionnaires to assess maternal mental health and healthy behaviors, which might involve response bias, possibly because of social desirability, which often obscures true differences between respondents (Lau et al., 2007). Data collection at five time points increased the power of the study, but the sample size of 40 might not have been sufficient to support combining the outcomes of self-report with biomarker measurement for assessing maternal mental health problems. It was not possible to run a power analysis before the study since it was a part of a larger study that set the sample size. Thus, the findings are potentially subject to lack of power or Type II error. Most mothers (95%) had received prenatal glucocorticoid treatment before birth, which was unavoidable. However, this treatment might not have affected maternal testosterone and cortisol levels because the effect of prenatal glucocorticoids lasts only about 7 days (Baud & Sola, 2007). Finally, we performed multiple analyses without adjusting the p value. This practice might have increased the chance of making Type I errors. On the other hand, adjusting the p value would have increased the chance of making Type II errors or needing to increase the sample size (Feise, 2002).

Because we found more maternal mental health problems at 24 months CA than before 12 months CA, future research should continue assessment beyond 24 months. Mothers might also experience more parenting difficulties when the infants show more socioemotional and behavioral problems after 24 months.

Findings of the present study further suggest that nurses in clinical practice should increase their focus on using self-report and/or biochemical measurement of salivary testosterone and cortisol levels to try to identify and address maternal mental health problems early in mothers at greatest risk, that is, mothers who are unmarried, have less education, have public health insurance, and have more medical complications during pregnancy. Early intervention from health-care providers among these mothers has the potential to reduce maternal mental health problems and parenting difficulties, benefiting not only the mothers but also their infants.

Conclusion

In the present study, we found that the combined use of self-report and biomarker measurement was effective in assessing maternal mental health and healthy behaviors over the 2 years after birth, when the mothers of VLBW infants experience more mental health problems and parenting difficulties than mothers of normal-BW full-term infants. Testosterone levels were more predictive for maternal mental health and healthy behaviors than cortisol levels. The negative associations between testosterone levels and maternal mental health and healthy behaviors were related to maternal demographic characteristics such as marital status, education, and type of health insurance. Finally, our findings provide support for nursing interventions that integrate screening for mental health and healthy behaviors into routine primary care for mothers who are at risk of poor mental health and parenting difficulties.

Author Contributions

June Cho contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the

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