



# Cortisol, Prolactin, and Breastmilk Volume; A Promising Pattern for Reducing Postpartum Depression

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## Abstract

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**BACKGROUND:** Research shows postnatal depression and shorter breastfeeding are consistently related, but their causal effect remains debatable. To reduce the impact of mental disorders in the perinatal period, lactation may give a significant neuroendocrine effect.

**AIM:** This study aimed to examine hormonal patterns and estimated breastmilk volume of mothers with depression.

**MATERIALS AND METHODS:** This study was conducted during the three-trimester to 6-week postnatal period. It involved 60 pregnant women from South Sulawesi, Indonesia. Analysis of variance with repeated measures was used to compare and review fluctuations and effect sizes of cortisol, prolactin, and breastmilk volume of mothers with depression symptoms.

**RESULTS:** The mean cortisol levels rose in the 4<sup>th</sup> week and decreased in the 6<sup>th</sup> week in both groups. There was no substantial difference in the cortisol levels between these periods ( $p = 0.534$ ;  $p = 0.553$ ; and  $p = 0.660$ ), but the prolactin levels continuously increased by 2 weeks and substantially progressed in the 4<sup>th</sup> and 6<sup>th</sup> weeks ( $p < 0.028$ ,  $p < 0.009$ ), respectively. There was no positive association between cortisol and prolactin levels ( $p = 0.384$ ). The breastmilk volume was higher every week only in mothers without depression and it slightly decreased in other categories. This study emphasized the prolactin's protective effect size on a stressful environment characterized by high cortisol; a significant rise in prolactin levels occurred in the 2<sup>nd</sup> and 4<sup>th</sup> weeks of postnatal, marking the higher lactation.

**CONCLUSIONS:** Breastfeeding hormones may provide protection against postpartum depression in moms. It is critical to establish a history of prior trauma in nursing mothers in order to facilitate diagnosis and proper care.

## Introduction

Both pregnant and postnatal mothers commonly experience mood disorder. Mood swing happens nearly every day in the forms of sadness, emptiness, hopelessness, and tearfulness. Such moods could be preliminary major depression symptoms. Peripartum depression is different from baby blues, which is characterized by short breastfeeding, mild symptoms, and minimal impact on mental health function. Women with peripartum depression have to undergo bipolar disorder, postnatal psychosis, and suicidal risk assessment [1]. Postnatal depression and shorter breastfeeding are consistently correlated, but their causal effect remains debatable [2], [3]. Breastfeeding is related to hormonal alteration such as a rise regulation of prolactin and down regulation of hypothalamic-pituitary-adrenal (HPA) axis. Research on brain shows that lactation could give neuroendocrine effects to modulate a stressful environment and reduce the impact of mental disorders during the perinatal

period [4], [5], [6], [7]. It happens because women of reproductive age most likely develop physiological disorders. A recent review reported about 0.89–2.6 in 1000 women had postnatal psychosis [8]. During postnatal depression, the HPA is activated since stress worsens physiological response to the human body [9], [10], [11], [12]. Cortisol levels increase normally up to 4 times in the last term of pregnancy along with corticotrophin releasing hormone-binding protein (CRH-BP) which prevent the pathways to activate [13]. The CRH-BP level decreases soon after birth and cortisol begins to express and function properly [14]. In early pregnancy, cortisol suppresses the inflammatory system and prevents it from fetus organ failure through the adrenal zona fasciculata pathway [15]. It also supplies the placenta, brain, and lungs and it is less responsive to acute stress. Cortisol also prepares the nature of nurturing behavior in mothers [16]. The secretion increases in the morning to noon and it decreases at night since it depends on sleep time pattern [17]. It means sleep and depression could be affected by cortisol change pattern [18]. Cortisol

levels will decrease average in 3 weeks and mothers might be susceptible of depression [19], [20]. Although perinatal depression may be caused by severe internal disorders, hypo and hypersensitivity of HPA-axis activity will predict certain postnatal depression symptoms [21].

Prolactin, on the other hand, is likely related to breastfeeding, stress modulation, and motherhood maturity hormone [22], [23]. The basal level increases during pregnancy and returns to average after 3 weeks, but it stays above the average in breastfeeding mothers compared to mothers with partial breastfeeding [6]. Prolactin works by producing, secreting, and maintaining breastmilk volume [24]. Stimulation and activation of breastmilk occur in mammary epithelial cells through the paraventricular nucleus signaling pathway [25], while the main synthesis pathway of proteins is activated through janus kinase-signal transducer and activation of transcription such as casein, lactoglobulin, and lactoferrin [26], [27]. Mothers who breastfeed longer will maintain lactation with a higher prolactin level [28]. In other circumstances, deficit or excessive prolactin after birth might cause maternal anxiety, motherhood malfunction, perinatal depression, and a lower milk supply [29], [30]. Stress due to environmental factors might increase reactivity in prolactin production, leading to an insufficient milk supply and early weaning [5], [12]. While research has been investigating the causal relationship between depression and breastfeeding, lactation may have significant neuroendocrine effects to modulate a stressful environment and reduce the impact of mental disorders during the perinatal and postnatal period. This preventive impact of breastfeeding could be the risk of developing mental disorders during the first 2 years of life. Most importantly, it is important to consider how the hormone cortisol and prolactin affect mothers with depression symptoms and how the interaction between these two hormones affects breastmilk production. According to the issues above, this study was aimed to examine the patterns of hormones and estimated breastmilk volume in breastfeeding mothers with depression symptoms.

## Materials and Methods

### *Research design and subject selection*

A longitudinal study was conducted from the third trimester up to 6 weeks of postnatal. It invited 60 eligible pregnant mothers who participated in an antenatal care program in one primary health-care provider in South Sulawesi, Indonesia. The monitoring on the mothers was followed up every 2 weeks after birth. The selected subjects were in part of baseline data from a previous published grant project [31]. The research was conducted from 2019 to 2021 [18]. The

current selected samples were recruited at the end of September 2020–January 2021. The findings of the study were compared with other previous studies to see the consistency or contradiction in the results [32].

### *Ethics*

Mothers were given sufficient explanation about the research purposes and procedures. Those who agreed to participate signed the informed consent form accompanied by their families (husband or grandmothers) and midwives in charge on the site. All of the procedures were approved by the Research Ethics Committee of Makassar Health Polytechnic No. 00737/KEPK-PTKMKS/X/2020.

### *Baseline data collection*

Data on sociodemographics, parity, and body mass index (BMI) were collected at the beginning of the research procedures using a validated instrument adopted from a previous study [18]. Sociodemographics contain seven questions regarding mother age, education, working status, monthly family income, housing, and numbers of family living under the same roof. Parity was related to the number of livebirths. BMI was measured from weight before pregnancy and classified as underweight, healthy, overweight, and obese [33].

### *Prolactin and cortisol measurement*

The amount of 3cc blood samples was obtained from the brachial vein shortly after birth by a trained laboratory assistant, and this protocol repeated at the end of 2 and 4 weeks of postnatal. Prolactin and cortisol serum levels were then determined using an enzyme immunoassay kit (Demeditec Diagnostics GmbH, Kiel, Germany for Cortisol ELISA DEH3388; Prolactin ELISA DE1291) as directed by the manufacturer.

### *Postnatal depression assessment*

Postnatal depression was assessed 3 times: at birth, at 2 weeks, and at 4 weeks after birth, using an expert-translated and validated Indonesian scales adopted from Edinburgh postnatal depression scale (EPDS) [31]. Postnatal depression is described as an EPDS score above 12. Mothers would be categorized into mothers with depression symptoms if the third measurement of EPDS on average was consistently above 12.

### *Breast milk production assessment*

Breastmilk volume was calculated using expressed breastmilk. Breastmilk pumping protocols were in accordance with the standard ethical procedures

and approved by the ethics committee. The mothers received multiple home visits using the Medela Swing Double Pump at 2, 4, and 6 weeks of postnatal. Pumping was taken in the morning between 7:00 and 9:00 a.m. once a day for about 15 min. The total of breastmilk volume was then multiplied by eight (the average frequency of breastfeeding per day) to estimate daily breastmilk productions [34]. Mothers performed regular breastfeeding practice and were monitored online through video conference on a WhatsApp group as in-person monitoring was restricted due to COVID-19.

**Statistics analysis**

All parameters were tested for the normality using the Kolmogorov–Smirnov. EPDS score, prolactin, cortisol, and breastmilk volume ( $p > 0.005$ ) were tested as well. The Chi-square test was used to analyze the baseline trait, followed by repeated measures analysis of variance to compare and review the fluctuations and effect size of cortisol level, prolactin level, and breast milk volume of breastfeeding mothers with depression symptoms.

**Results**

The homogeneity between the groups was similar based on the Chi-square continuity correction as indicated in Table 1. Mothers with depression symptoms (average score of EPDS greater than 12) made up 46.6% of the total subjects. The groups were most likely low socioeconomic families. The dominant mothers' education was senior high school ( $p = 0.370$ ); it was

the first time experience of being a mother ( $p = 0.342$ ) and housewives ( $p = 0.361$ ) for most of them. Most of them had a lower income of less than IDR 3 million or \$ 214.28 ( $p = 0.369$ ) per month.

The subjects were nuclear families ( $p = 0.673$ ) who rented houses ( $p = 0.929$ ). Nuclear families are married couples who live solely with their children, while extended families include more than one family member, such as a grandmother, grandfather, mother's relatives, or father's relatives. The data showed no difference in BMI ( $p = 0.771$ ); however, it was a quite alarming percentage in overweight and obese among 41.6% of the mothers. Unhealthy pre-pregnancy was likely to be caused by BMI consider as one contributing risk in increasing anxiety and serious mental illness during postnatal [35]. Overall, there was no significant difference in all of these sociodemographics between two group.

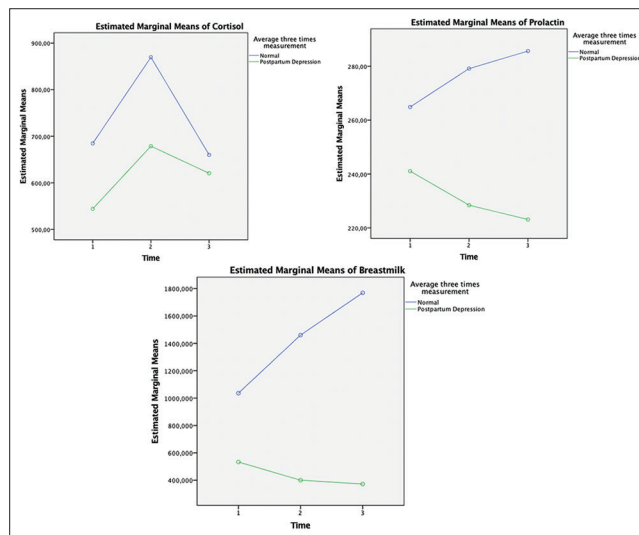
Table 2 shows the difference in cortisol level, prolactin level, and breastmilk volumes over time. Mean cortisol levels in both groups increased in the 4<sup>th</sup> week and decreased in the 6<sup>th</sup> week without significant difference between intervals ( $p > 0.149$ ). Prolactin levels in mothers without depression symptoms rose steadily over 2 weeks but reached the peak at the 4<sup>th</sup> and 6<sup>th</sup> week ( $p \leq 0.001$ ). Weekly breastmilk volume was higher in non-symptomatic mothers and slightly lower in the other group. The interaction (group x time) of depression symptoms affected fairly of 0.269 on prolactin and 0.617 on breastmilk volume.

Prolactin levels and estimated breastmilk volume likely contributed to the risk of depression symptoms. Figure 1 shows a difference point in measurement intervals between cortisol level, prolactin level, and breastmilk volume. Prolactin levels and estimated breastmilk volume were higher in non-depressive mothers. Although cortisol levels between the groups were comparable, surprisingly mothers with depression symptoms had lower cortisol levels. These

**Table 1: Sociodemographics of research subjects**

Characteristics	EPDS ≤ 12 (n = 32)		EPDS > 12 (n = 28)		p*
	n	Percentage	n	Percentage	
Age (years)					0.955
≤ 19	1	50.0	1	50.0	
20–30	18	48.6	19	51.4	
≥ 31	13	61.9	8	38.1	
Education					0.370
Postgraduate	6	42.9	8	57.1	
Undergraduate	26	56.5	20	43.5	
Parity					0.342
Multiparous	11	45.8	13	54.2	
Primiparous	21	58.3	15	41.7	
History of abortion					0.346
Yes	1	100.0	0	0.0	
No	31	52.5	28	47.5	
Pre-pregnancy BMI					0.771
Underweight	4	57.1	3	42.9	
Normal	17	58.6	12	41.4	
Overweight	10	47.6	11	52.4	
Obese	1	33.3	2	66.7	
Working mothers					0.361
Yes	4	36.4	7	63.6	
No	28	57.1	21	42.9	
Family income					0.369
≥ Wage standard	15	62.5	9	37.5	
< Wage standard	17	47.2	19	52.8	
Family type					0.673
Nuclear	20	55.6	16	44.4	
Extended	12	50.0	12	50.0	
Living in					0.929
Private/permanent house	6	54.5	5	45.5	
Rent/temporary house	26	53.1	23	46.9	

\*Chi-square test. BMI: Body mass index, EPDS: Edinburgh Postnatal Depression Scale.



**Figure 1: The difference pattern of cortisol level, prolactin level, and breastmilk volume between measurement intervals**

**Table 2: Results of repeated measures ANOVA between measurement intervals (n = 60)**

Indicators	EPDS ≤ 12 (n = 32)						EPDS > 12 (n = 28)						F	p	Effect size
	T1		T2		T3		T1		T2		T3				
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD			
Cortisol	684.8	227.9	869.7	289.4	660.2	144.7	544.2	254.2	678.7	316.2	620.7	101.3	2.140	0.149	0.036
Prolactin	264.8	102.5	279.1	103.0	285.6	103.1	241.0	88.3	228.4	93.9	223.1	97.6	21.316	≤ 0.001	0.269
Breastmilk volume	1036.3	683.8	1460.4	918.7	1768.9	1100.8	533.0	547.7	400.6	475.7	372.0	442.2	93.248	≤ 0.001	0.617

F values (group\*time measurement) for repeated-measures ANOVA test, df = 1. T1: First measurement, T2: Second measurement, T3: Third measurement. SD: Standard deviation, EPDS: Edinburgh Postnatal Depression Scale.

results indicate that prolactin level could protect mothers from depression and motivate them to continually breastfeed. Since prolactin levels only slightly decreased over time, a periodical score of EPDS >12 in mothers with depression symptoms did not always have a strong impact on lowering breastmilk volume. In this case, we confirm that during breastfeeding, mothers who exhibit depressive symptoms can be protected from breastfeeding failure by maintaining high prolactin levels for lactational function.

## Discussion

In this study, women either with or without depression symptoms had higher cortisol levels at the 1<sup>st</sup>-2<sup>nd</sup> week and lower at the 4<sup>th</sup> week. Interestingly, women without depression symptoms had overall higher cortisol levels in all measurement intervals. By the end of 4<sup>th</sup> week, both mothers with and mothers without depression symptoms demonstrated a slight difference in mean cortisol levels of 660 µg/ml and 620 µg/ml, respectively. Given that both groups were still fully breastfeeding, the higher cortisol levels may be a response to a stress-increasing environment in the early period of breastfeeding that correlates with increased prolactin levels in the second and third measurements. Higher prolactin levels were also accompanied by an increase in breastmilk volume in both groups. Increased levels of prolactin and lactation are physiological mechanisms of breastfeeding [36], [37], [38]. In a stressful environment, a nursing mother will continue to breastfeed and produce milk without disrupting the lactation cycle by high cortisol levels. It is too early in this study to confirm that a decrease in cortisol levels at the 4<sup>th</sup> week has an impact on prolactin or prolactin triggers a decrease in cortisol levels at week 4 despite the correcting effect of lactation in hypercortisolemic pregnancies [10]. Lactation has been reported to ameliorate physiologic hypercortisolism in pregnancy and maintain the downregulation of HPA axis activity that occurs after delivery. Maternal levels of adrenocorticotrophic hormone (ACTH) and cortisol drop dramatically when the baby start to suckles the nipple for the first time [6], [7]. This study demonstrates promising protection from exclusive breastfeeding in a stressful environment. Another study in 741 women found consistently lower cortisol levels at wake and at night in breastfeeding women compared to non-breastfeeding or nulliparous women up to 1 year after delivery [39].

Breastfeeding is also associated with decreased HPA axis reactivity during physical stress and psychosocial condition in postnatal mothers [40], [41]. Mothers who breastfeed show a sharp decrease in cortisol peaks in the morning to lows in the evening compared to those who do not breastfeed [42], [43]. In this study, there was a sharp decrease in cortisol levels measured in the morning during the 2<sup>nd</sup> and 4<sup>th</sup> weeks in both groups regardless of the different stress conditions thought to influence intense lactation. A similar study [42] has also shown that higher cortisol trajectories are associated with deleterious physical and psychosocial conditions. In other words, breastfeeding can optimize the circadian rhythm of cortisol secretion. Many studies have found a role for breastfeeding in endocrine regulation through higher levels of prolactin and oxytocin. As a result, the secretion of androgens, estrogens, vasopressin, and glucocorticoid ACTH is lower. This reverse condition reduces the risk of postnatal destructive psychology. In addition, prolactin may contribute to stress control through downregulation of prolactin receptors in lactating mice [44]. Expression of the prolactin receptor gene was also found to be higher in mothers who had more breastmilk volume and breastfeeding intensity [45], [46]. Downregulation of prolactin receptors enhances responses to anxiety through the increase in ACTH release; however, administration of prolactin to female rats causes hyperprolactinemia, giving anxiolytic effects and triggering the suppression of ACTH, corticosterone, and noradrenaline [47]. The anxiolytic role of prolactin answers the mechanism of lactation on the activation of the HPA axis. High circulating prolactin levels, which likely increase consecutively, will increase the duration and reduce deep sleep disturbances that occur slowly [48], [49], while one of the risk factors for depression is poor sleep quality in mothers [18]. At the end of breastfeeding, there is a reversal control of dopamine tonic inhibitors [50], [51]. In breastfeeding mothers with a history of depression in adolescence when high dopamine levels trigger symptoms of manic depression and psychosis [52]. Mothers with a history of depression who weaned prematurely were more likely to have a more severe depressive disorder. Low dopamine levels because of the mechanism of prolactin are likely a protector against psychosis symptoms in breastfeeding mothers. However, the validation of dopamine and postnatal psychosis needs more comprehensive clinical research. This study has delineated the relationship of the hormonal pattern of cortisol, prolactin, and breastmilk volume through

standardized repeated measurements. This study emphasized the prolactin's protective effect size on a stressful environment characterized by high cortisol; a significant rise in prolactin levels occurred in the 2<sup>nd</sup> and 4<sup>th</sup> weeks of postnatal, marking the higher lactation.

### Limitation

The depression symptoms were solely measured using the repeated and validated EPDS method and they may differ subjectively from the diagnosis and clinical measurement. As a result, the genuine clinical context of acute or chronic depression disorder in the postnatal period cannot be confirmed by this investigation. However, the study was unable to determine the long-term influence of postnatal depression on childbearing outcomes such as child growth, especially among mothers who reported weaning after 6 weeks of online monitoring.

### Conclusion

Breastfeeding hormones may protect mothers from postnatal depression. Mothers who are prone to postnatal depression should be encouraged to breastfeed for a longer period. It is critical to discover mothers with prenatal depression symptoms as early as possible through a history of depression during adolescence and childhood trauma. Therefore, preventive treatments and better breastfeeding quality are required.

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### Authorship Contribution Statement

A.S. planned and drafted the text, analyzed the data, and wrote the article. A.K. was responsible for field data collection and quality assessment, I.I. was responsible for online monitoring and follow-up throughout the research, and M.Q. was in charge of analysis and data acquisition. All of the authors read and approved the final article.

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