KEMAS 18 (4) (2023) 571-579

Jurnal Kesehatan Masyarakat

http://journal.unnes.ac.id/nju/index.php/kemas

Maternal Anxiety and Sleep Quality Affects of Neonatal Brain-Derived Neurotrophic Factor

Amel Yanis[1]✉, Rahmi Andrita Yuda[2], Hudila Rifa Karmia[3]
[1]Department of Psychiatry, Faculty of Medicine, Andalas University
[2] Master Program Of Midwifery, Faculty of Medicine, Andalas University
[3] Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University

Article Info

Article History:
Submitted November 2022
Accepted January 2023
Published April 2023

Keywords:
BDNF, Maternal Anxiety, Sleep Quality

DOI
https://doi.org/10.15294/kemas.v18i4.40241

Abstract

Anxiety conditions and sleep disorders in pregnant women will affect the Brain-Derived Neurotrophic Factor (BDNF) level of the baby's umbilical cord blood, which will then affect the growth and development of the baby. This study aims to assess the relationship between maternal anxiety and sleep quality with neonates' BDNF levels. The research design was a cross-sectional study. Pregnant Women who gave birth by cesarean delivery method with a gestational age of ≥ 37 weeks, Totally 78 pregnant women involved. Anxiety levels and sleep quality were assessed by questionnaire, and BDNF levels were taken from the umbilical cord blood and then checked using the ELISA method. Data were analyzed by One-Way-Anova and Independent T-test. There was a significant association between anxiety levels and sleep quality with Neonatal BDNF levels (p = 0.000). The results obtained for pregnant women without anxiety, the mean level of BDNF is 2.017 ± 0.138 ng /ml. Mild anxiety, the mean value of BDNF level is 1.792 ±0.134 ng/ml. Moderate anxiety, the mean value of BDNF level is 1.708±0.177 ng/ ml. Severe anxiety, the mean value of BDNF levels was 1.585±0.257 ng/ml . Pregnant women with good sleep quality had the mean BDNF level of 1.969±0.211 ng/ml, while the mean BDNF level of poor sleep quality was 1.673 ±0.188 ng/ml. Conclusion: The higher the anxiety level of pregnant women, the lower the average Neonatal BDNF level is. The worse the sleep quality of pregnant women, the lower the average Neonatal BDNF level is.

Introduction

The future of a nation depends on the success of children in achieving optimal growth and development. The fetal period, the first years of life, is essential in the growth and development of children (Kemenkes, 2016). The development of a child's nerves and brain occurs from the moment in the womb, namely the embryonic period, to prenatal and postnatal. The prenatal and postnatal periods are critical periods in which the fetal brain can be changed and shaped(De Vincenti, Ríos, Paratcha, & Ledda, 2019). World Health Organization reported that 10% of children experience developmental and emotional disorders(WHO, 2021). Global research conducted in 195 countries by Olusanya et al. (2018) in The Lancet Series on child development disorders also reported an increased potential for developmental disorders in as many as 632 million children under five years. These child development problems include delays in motor development, language development, autism, hyperactivity, cognitive and intellectual disorders, and emotional disorders (Herba, Glover, Ramchandani, & Rondon, 2016; Olusanya et al., 2018).

Developmental disorders in children under five years occur primarily in developing and low-income countries, with a prevalence of more than 50 million (Olusanya et al., 2021). The majority of cognitive and socio-emotional

✉ Correspondence Address:
Department of Psychiatry, Faculty of Medicine, Andalas University, Indonesia.
Email : amelyanis@med.unand.ac.id

pISSN 1858-1196
eISSN 2355-3596

developmental disorders in children under five years in the South and Southeast Asia region was 31.5%. Cognitive and socio-emotional developmental disorders in children under five years in Indonesia were 23.8% (Langgapin, Sirithongthaworn, Yang, & Reddy, 2019). The interference problem of the development of children under five years in Indonesia is still severe, consisting of 701 cases of autism per 100,000, intellectual development disorders as many as 1,244 per 100,000, hyperactive children as many as 85 per 100,000(Langgapin et al., 2019). Developmental disorders in children can be affected by the formation of neural circuits and suboptimal brain development that starts in the prenatal period (Kadic & Kurjak, 2018). The process of neurogenesis is influenced by several proteins that stimulate neurons' growth, development, plasticity, and endurance. This group of proteins is neurotropic. One of the neurotrophic groups that has an essential role is the Brain-Derived Neurotrophic Factor. BDNF is expressed in the hippocampus, cortex, cerebellum, and amygdala (De Vincenti et al., 2019).

Research by Ghassabian et al. (2017) stated that high Brain DeriBrain-Derivedhic Factor (BDNF) levels could significantly reduce failures in child development. Low neonatal Brain-Derived Neurotrophic Factor is associated with developmental domain failure (Ghassabian, 2017). A study by Skogtrand et al. (2019) stated that reducing BDNF levels in newborns could significantly increase the occurrence of neurodevelopmental disorders by 1.15 times higher than in normal conditions (Skogstrand et al., 2019). Low levels of Brain-Derived Neurotrophic Factor can affect brain development, causing hippocampal atrophy. Hippocampal atrophy will impact the development and intelligence level (Scheinost, Spann, McDonough, Peterson, & Monk, 2020).

Brain-Derived Neurotrophic Factor levels in the fetus are influenced by the intrauterine environment and psychosocial stressors (Flock et al., 2016; Herba et al., 2016). Fetal exposure to psychological disorders in pregnant women can interfere with optimal brain development. Psychological disorders can induce epigenetic modifications in BDNF, resulting in changes in BDNF gene expression (K. W. Chen & Chen, 2017). Research by Fung et al. (2015) stated that anxiety and stress disorders experienced during pregnancy or before delivery could cause a decrease in cord BDNF levels 1.6 times lower than in healthy mothers(Fung et al., 2015). Sonmez et al. (2019) showed that cord blood BDNF levels in mothers who experienced anxiety and depression were significantly lower than cord blood BDNF levels in infants of healthy mothers. BDNF levels decreased from 2.08 ng/ml to 0.98 ng/ml(Sonmez et al., 2019).

The results of a study by Monteiro et al. (2017) stated that someone with anxiety and stress disorders often experiences sleep disturbances. Poor sleep quality can also cause stress, suppressing the secretion of Brain-Derived Neurotrophic Factors. This study stated that there was a causal pattern between sleep deprivation, BDNF levels, and depression (Monteiro et al., 2017). Sleep disturbances can modulate stress and then activate the hypothalamus-pituitary-adrenal (HPA) axis, which causes an increase in cortisol secretion. Increased cortisol concentration can suppress BDNF production (Fan et al., 2019). In line with research conducted by Kriengtuntiwong, Zaw et al. (2021) in Thailand stating that apart from stress and anxiety levels, BDNF levels were also affected by sleep quality. Research by Fan et al. (2019) said that poor sleep quality makes BDNF levels three times lower than those with good quality sleep (Fan et al., 2019). In contrast to the results of the study by Deuschle et al. (2018), which stated that there was no significant difference in BDNF levels in patients with sleep disorders(Deuschle et al., 2018).

The intrauterine environment and psychosocial stressors influence developmental disorders in children in the womb. Still, health workers focus more on prevention, treatment, and intervention in pregnant women's physical and intrauterine environments. Psychological problems and sleep disturbances are often overlooked and rarely given attention. Many studies have assessed the relationship between BDNF levels and other factors in pregnant women. Research examining the relationship between psychological disorders (anxiety level and sleep quality) and BDNF levels of the baby's umbilical cord blood in mothers giving birth is rarely done in Indonesia. Based on this,

the researchers were interested in conducting this study to determine whether there is a relationship between anxiety levels and brain levels (BDNF) of the baby's umbilical cord blood in mothers giving birth.

Methods

This research was an observational study with a cross-sectional design. It took time from November 2021 to June 2022 and was approved by the Andalas University research ethics committee with number 677/UN.16.2/KEP-FK/2022. The inclusion criteria in this study were women giving birth with a gestational age ≥37 weeks with the Caesarean section delivery method without complicating diseases and willing to participate as research subjects. Exclusion criteria in this study were pregnant women with pre-eclampsia/eclampsia, pregnant women with diabetes, pregnant women who were obese, pregnant women with systemic infections, pregnant women with anemia, pregnant women who were active smokers, and pregnant women who consumed alcohol.Patients who met the requirements were identified as research subjects through collaboration in three medical institutions in Padang, West Sumatra, Hermina Hospital, Reksodiwiryo Hospital, Andalas University Hospital. To determine the minimum sample size, a sample size formula was used for single population data to estimate the average (Hardisman, 2021).

$$n = \frac{Z\alpha^2 \times S^2}{d^2}$$

Based on the procedure and standard deviation, we got a large sample, namely 78 respondents. Maternity mothers who met the requirements and agreed to participate in this study signed informed consent. Anxiety level assessment used the Zung Self Anxiety Scale questionnaire. Evaluation of sleep quality using the Pittsburgh Sleep Quality Index (PSQI) questionnaire, was carried out when the mother was in the obstetrics/delivery room before delivery, then taking the baby's cord blood from the maternal department in the operating room during the process of cesarean section delivery. After the baby's umbilical cord blood was obtained, we processed it with a centrifuge (separating the blood into serum). After all the samples were collected, the BDNF levels were checked at the Biomedical Laboratory, Andalas University, Padang, using the enzyme-linked immunosorbent assay (ELISA) method. The One Way Anova statistical test was used to assess the relationship and differences between anxiety levels and the average BDNF level. In contrast, the T-Independent test was used to determine the relationship between sleep quality and cord blood BDNF levels using the SPSS version 26 program.

Results and Discussion

Based on Table 1, the results of statistical analysis showed that of the 78 pregnant women nearing delivery at the Padang city hospital, 12 (15.4 %) pregnant women did not experience anxiety, then the statistical results showed that there were 66 (84.6%) pregnant women who experienced anxiety. Pregnant women who experienced anxiety consisted of 8 pregnant women (10.3%) with mild anxiety, 34 pregnant women (43.6%) experienced moderate, and as many as 24 pregnant women (30.6%) experienced severe anxiety. It shows that many pregnant women experience psychological disorders, especially anxiety problems, in Padang city hospitals. It was known that of 78 pregnant women nearing delivery at the Padang city hospital, 15 women (19.2%) experienced good sleep quality. As many as 63 pregnant women (80.8%) experienced poor sleep quality in Padang City Hospital.

Table 1. Frequency Distribution of Anxiety Levels and Sleep Quality in Pregnant Women at Several Hospital in Padang City

Anxiety Levels	**F**	**(%)**
Without Anxiety	12	15.4
Mild Anxiety	8	10.3
Moderate Anxiety	34	43.6
Severe Anxiety	24	30.7
Total	78	100%
Sleep Quality		
Good	15	19,2
Poor	63	80,8
Total	78	100%

Table 2. The Relationship between anxiety levels and Neonatal BDNF levels

Anxiety Level	Neonatal BDNF Level				p- *Value*
	n (%)	Mean	SD	F	
No Anxiety	12(15.4)	2.017	0.138	16,196	0.000
Mild Anxiety	8(10.3)	1,792	0.134		
Moderate Anxiety	34(43.6)	1,708	0.177		
Severe Anxiety	24(30.7)	1.585	0.207		
Amount	78(100%)	**1,726**	**0.224**		

Table 3. The Relationship between Sleep Quality and Neonatal BDNF Levels

Sleep Quality	Neonatal BDNF Level				P *Value*
	n(%)	Mean	SD	T	
Poor	15(19.2)	1,673	0.188	-4,851	0.000
Good	63(80,8)	1,949	0.199		
Total	78(100)				

One-Way-Anova statistical analysis showed a difference in anxiety level with the average Brain-Derived Neurotrophic Factor (BDNF) level. So, we can conclude a significant relationship between the anxiety level and Brain-Derived Neurotrophic Factor (BDNF) levels in cord blood baby centers for mothers giving birth. It can be seen from the p-value < 0.05, namely p = 0.001. Where the higher the level of anxiety of the study subjects, the lower the average BDNF level is.

T-Independent analysis results, different tests on the average BDNF levels based on the sleep quality group, showed differences in the mean Brain-Derived Neurotrophic Factor (BDNF) levels based on the sleep quality group. We can conclude that there is a significant relationship between sleep quality and the levels of Brain-Derived Neurotrophic Factor (BDNF) in the baby's umbilical cord blood in mothers giving birth. It can be seen from the p-value < 0.05, namely p = 0.000. Where the poorer the quality of sleep of the study subjects, the lower the average BDNF levels.

From the results of the study, we know that many pregnant women experience psychological disorders, especially anxiety problems, at the Padang city hospital. In this study, the researchers used the Zung self-anxiety scale research instrument to assess maternal anxiety. The questions in this questionnaire already described somatic symptoms and psychological symptoms. Research subjects (pregnant women) who experienced anxiety in this study were followed by somatic clinical symptoms such as many pregnant women experiencing respiratory problems, digestive disorders, dizziness, palpitations, paleness, fatigue, and others. In addition, in this study, research subjects who experienced anxiety were also followed by psychological problems, such as irritability, more sensitivity, crying easily, anxiety, feelings of worry, lack of enthusiasm, and feelings of excessive fear.

The results of the study by Luo et al. (2022) explained that risk factors that were significantly related to depression and anxiety in pregnant women during the COVID-19 pandemic were the age of pregnant women, education level, number of children/parities, employment status, chronic disease, physical activity, social support and family income (Luo, Zhang, Huang, & Qiu, 2022). Research by S. Chen, Zhuang, Chen, & Tan (2020) reported that what caused anxiety during pregnancy was 72.67% of anxiety caused by fear of whether the child could be born safely and smoothly, 38.1% of anxiety about the pain of labor, anxiety about changing roles, figures, and activities after giving birth 18.79%, anxiety about the possibility of being infected with the COVID-19 virus 18.62%, anxiety because economic pressure after giving birth 18.02%, the anxiety of not being able to take care of children and work at the same time was 16.98% (S. Chen, Zhuang, Chen, & Tan, 2020). In line with the results of research that researchers conducted in several hospitals in the city of Padang, where it was

found that pregnant women experience anxiety caused by anxiety related to their pregnancy, anxiety related to their health, concern about labor pains, worry about the health of their unborn child, especially during the COVID-19 pandemic. They were more afraid to leave the house, interact with others, and carry out social activities.

The anxiety problem is because many pregnant women fear the physical changes they experience, such as excessive weight gain during pregnancy. Pregnant women are often anxious to fulfill responsibilities, and their role as a parent is related to work and the number of children they have. Mothers who have never had children before tend to experience more anxiety about physical changes and changes in roles and responsibilities than mothers who have had children before. In contrast, multigravida mothers often experience anxiety caused by many children or the close age gap, as well as the age factor that causes them to worry about not being able to take care of their children properly.

Meanwhile, social problems can be caused by a lack of support and attention from husbands, family support, and social support for pregnant women. In addition, anxiety is also influenced by financial problems, especially during the COVID-19 pandemic affecting family income. Some respondents who did not have jobs and were unstable and low-income tended to be more anxious. Meanwhile, working mothers also experience anxiety because they are worried they can't take good care of their babies. Anxiety during pregnancy is also because of obstetric history or bad experiences related to previous pregnancies. Mothers with previous poor obstetric history tend to experience anxiety. They are afraid of the baby's condition and its condition. In addition, we also found that the age factor influences it. Women younger or older during childbirth are more prone to anxiety problems related to their physical condition and coping mechanisms.

The results of the One-Way-Anova analysis, different tests on the average BDNF levels based on the anxiety level group. Where the average level of BDNF was higher in the group without anxiety at 2.017 ± 0.138 ng/ml, followed by the average level of mild anxiety at 1.792 ± 0.134 ng/ml, the average level of BDNF in moderate anxiety level 1.708 ± 0.177 ng/ml, and with the lowest mean BDNF levels were in the group with severe anxiety levels, namely 1.585 ± 0.205 ng/ml. It showed a significant relationship between anxiety levels and Brain-Derived Neurotrophic Factor (BDNF) levels in babies' umbilical cord blood in mothers who gave birth. We can see from the p-value < 0.05, $p = 0.000$.

Mothers who experience anxiety, stress, and depression during pregnancy can result in disturbances of monoamine neurotransmitters and decreased serotonin which can trigger inflammatory reactions and suppress BDNF levels. In addition, there is an increase in maternal glucocorticoid levels or cortisol levels of the fetus(McGowan & Matthews, 2018). In line with recent studies showing that the hypothalamic pituitary adrenal (HPA) axis plays a role in mediating the effects of maternal anxiety and stress on the fetal brain. Prolonged stress exposure causes disruption of the HPA axis and then increases the concentration of glucocorticosteroids/cortisol in the blood and has a negative/destructive effect on cells of the nervous system, which can stimulate a decrease in BDNF levels. Low levels of BDNF can cause the hippocampal volume to decrease and cause neurodevelopmental disorders (Murawska-Cialowicz et al., 2021).

Neurobiologically, anxiety causes noradrenergic, GABAergic, and serotonergic disturbances and involves the frontal lobe and limbic system. The higher the level of anxiety, the lower the BDNF level is. It indirectly affects cognitive parameters, including spatial learning and memory, as well as the emotional development of the fetus in the future (Porcher, Medina, & Gaiarsa, 2018). Miguel et al. (2019) showed a decrease in volume and thickness in the frontal, temporal, and limbic areas (with MRI) and an increase in frontal activation in children whose mothers had higher prenatal anxiety. In addition, there is more excellent functional connectivity between the amygdala and the left temporal cortex, indicating an acceleration of the connectivity pattern observed in people with anxiety or depressive disorders (Miguel, Pereira, Silveira, & Meaney, 2019).

Christian et al.'s study (2016) showed that

maternal BDNF levels at the circulation level were the same as fetal brain levels. These data support that if the mother experiences anxiety and depression, the BDNF levels will decrease, affecting the fetal BDNF levels. It shows that mood, anxiety, and stress affect BDNF levels (Christian, Mitchell, Gillespie, & Palettas, 2016). This study also shows that pregnant women in their third trimester or near delivery are prone to experience anxiety and depression, which can induce changes in BDNF levels.

Mothers who experience anxiety, stress, and depression during pregnancy can result in disturbances of monoamine neurotransmitters and decreased serotonin which can trigger inflammatory reactions and suppress BDNF levels and cytokine release by microglia. Anxiety and stress reduce the production of TNF-α and interleukin-1β (IL-1β) while also increasing the output of pro-IL-1β, IL-6, and TNF-α. Psychosocial stressors can activate the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nerves, then glucocorticoids and noradrenaline increase in the brain. Glucocorticoids and noradrenaline regulate cytokine release from microglia. Glucocorticoids suppress cytokine release from microglia by suppressing NF-Kb. Stress reduces BDNF expression in the hippocampus and prefrontal cortex. One of the mechanisms that cause a decrease in BDNF is caused by an inflammatory reaction, namely microglial, due to a reduction in the binding of cAMP response element binding protein to the promoter area of the BDNF gene due to excessive NF-κB activation (Enomoto, 2022).

Symptoms of maternal anxiety and depression increase the child's risk of experiencing various emotional, behavioral, and cognitive problems, which can affect the brain and behavior of future offspring. The results also report maternal anxiety and stress are associated with changes in limbic and frontotemporal networks and functional and microstructural connections present in the brain (Lautarescu, Craig, & Glover, 2020). Psychological disorders such as stress, anxiety, and chronic depression reduce the expression of BDNF, increase apoptosis and decrease the regeneration of neurons in the hippocampus, and reduce the expression of BDNF in the brain.

In addition to anxiety problems in pregnant women, out of 78 pregnant women respondents who were nearing the time of delivery at the Padang City Hospital, 15 pregnant women (19,2.%) experienced good sleep quality, then 63 pregnant women (80.8%) experienced poor sleep quality at the Padang city hospital. Then, we concluded that many pregnant women experienced poor sleep quality at the Padang city hospital. Based on the results of research related to the assessment of sleep quality for mothers in labor using the Pittsburgh Sleep Quality Index questionnaire, which not only assesses sleep quality and sleep duration but also sleep latency, sleep efficiency, sleep disturbances, dysfunction of daytime activities, and use of sleeping pills. In this research, the researchers found that many pregnant women have poor sleep quality, and their sleep duration was less than 7 hours.

Many pregnant women experience sleep latency disorders or difficulty getting to sleep. Most pregnant women say it is difficult to start sleeping because they have physical problems such as shortness of breath, low back pain, difficulty finding a comfortable position, and frequent urination. Pregnant women find it difficult to start sleeping due to psychological problems such as experiencing anxiety, thoughts, and fears related to pregnancy or other personal issues. Hence, they divert by playing on their mobile phones, making it more difficult to fall asleep. The sleep efficiency of pregnant women is also disrupted. They often wake up at night because they need to urinate or because the mother still has a toddler and the discomfort of other physical changes related to pregnancy. From the research results, no pregnant women used sleeping pills to fall asleep. Despite the short amount of sleep they were getting, they were still trying to fall asleep naturally.

A statistical analysis of the Independent T-test showed that pregnant women with good sleep quality had an average BDNF level of 1.949 ± 0.199 ng/ml. In comparison, poor sleep quality had an average BDNF level of 1.673 ± 0.188 ng/ml. There was a difference in the mean BDNF levels in the sleep quality category, where the worse the sleep quality of pregnant women, the lower the BDNF levels

were. It could be concluded that there was also a significant relationship between sleep quality and infant cord blood BDNF levels (p=0.00). In line with the study of Monteiro et al. (2017) that serum BDNF levels were related to sleep. Sleep disturbances can cause physical and mental problems because sleep deprivation is usually followed by increased susceptibility to stress, which can reduce BDNF production(Monteiro et al., 2017). Lack of sleep is often followed by higher stress susceptibility, reduced environmental adaptation, and cognitive impairment; this is caused by disruption of various endocrine, physiological, and nervous functions (Giese et al., 2013).

Brain-Derived Neurotrophic Factor (BDNF) plays a role in sleep homeostasis. An interaction was found between stress, anxiety disorders, and sleep disturbances affecting serum BDNF levels. This result was in line with the assumption that stress or anxiety affects sleep and BDNF levels and vice versa sleep impacts the relationship between stress and BDNF (Giese et al., 2013). This study also indicated that sleep is a crucial mediator between stress and BDN. Sleep quality is highly correlated with symptoms of depression and anxiety disorders. A person with poor sleep quality can activate the HPA axis response to physical and psychosocial stressors.

The HPA axis is also linked to stress, anxiety, and depression, which leads to corticotropin (ACTH) release from the pituitary gland and cortisol from the adrenal glands. Sleep disturbances and depression may participate in the manifestation of an abnormal HPA axis and elevated cortisol levels.This increase in cortisol levels can suppress the production of BDNF levels (Bao et al., 2022). Brain-Derived Neurotrophic Factor (BDNF) can influence sleep quality by binding to TrkB, which sends signals to the pedunculopontine tegmental nucleus, which plays an essential role in developing REM sleep homeostasis. An animal study showed a significant positive relationship between REM sleep homeostatic drive and BDNF expression levels (Kriengtuntiwong, Zaw, & Taneepanichskul, 2021).

According to the research that researchers have done, many pregnant women say they often experience sleep disturbances caused by the workload during pregnancy, which makes them sleep less, the number of children, and the spacing of children. In addition, many pregnant women have toddlers, so they often wake up when the toddlers cry and wakefulness. Sleep disturbances also often occur due to the increasing gestational age, so physical and hormonal changes during pregnancy cause discomfort during sleep. Furthermore, pregnant women are prone to experiencing sleep problems during pregnancy which are closely related to depression and anxiety because they think about pregnancy conditions, economic issues, work problems, and social problems. Therefore, sleep must be considered because sleep problems are closely related to pregnancy-related psychological issues that impact pregnant women's welfare and their fetuses.

Conclusion

Pregnant women who do not experience anxiety have higher levels of BDNF in their baby's cord blood than pregnant women who experience anxiety. The higher the anxiety level of pregnant women, the lower the level of BDNF in the cord blood of the baby they have. This proves that psychological problems affect BDNF levels in the baby's cord blood. Based on the research results that the researchers have done, it was also found that if the quality of the mother's sleep during pregnancy is good, it can increase the baby's BDNF levels. However, if a mother's sleep during pregnancy is poor, this can lower BDNF levels. Good sleep quality is thought to handle stress and overcome mental disorders. A lack of quality sleep makes one prone to stress and anxiety and can increase cortisol production; thus, the BDNF level is also affected and decreases. The low neonatal BDNF levels are due to symptoms of anxiety and sleep disturbances. It can increase the risk of neurodevelopmental disorders, with decreased hippocampal volume in the brain, cognitive impairment can experience various emotional problems, and future hereditary behavior. Based on these findings, it is hoped that health workers, especially midwives, will improve the quality of ANC so that they do not only focus on physical and obstetric care but also increase promotive, preventive, and

even support efforts related to psychological problems and sleep disturbances in pregnant women during antenatal care visits.

References

Bao, C., Jin, D., Sun, S., Xu, L., Wang, C., Tang, W., Zhang, W., Bao, Y., Xu, D., Zhou, S., Yu, X., & Zhao, K., 2022. Trajectories and Depressive Symptoms During the Perinatal Period: A Longitudinal Population-Based Study in China. *Front Psychiatry,* 13, pp.762719.

Chen, K.W., & Chen, L., 2017. Epigenetic Regulation of BDNF Gene during Development and Diseases. *Int J Mol Sci*, 18(3).

Chen, S., Zhuang, J., Chen, Q., & Tan, X., 2020. Psychological Investigation on Pregnant Women during the Outbreak of COVID-19. *Europe PMC*, 2020.

Christian, L.M., Mitchell, A.M., Gillespie, S.L., & Palettas, M., 2016. Serum Brain-Derived Neurotrophic Factor (BDNF) Across Pregnancy and Postpartum: Associations with Race, Depressive Symptoms, and Low Birth Weight. *Psychoneuroendocrinology,* 74, pp.69-76.

De Vincenti, A.P., Ríos, A.S., Paratcha, G., & Ledda, F., 2019. Mechanisms That Modulate and Diversify BDNF Functions: Implications for Hippocampal Synaptic Plasticity. *Frontiers in Cellular Neuroscience,* 13, pp.135.

Deuschle, M., Schredl, M., Wisch, C., Schilling, C., Gilles, M., Geisel, O., & Hellweg, R., 2018. Serum Brain-Derived Neurotrophic Factor (BDNF) in Sleep-Disordered Patients: Relation to Sleep Stage N3 and Rapid Eye Movement (REM) Sleep Across Diagnostic Entities. *J Sleep Res,* 27(1), pp.73-77.

Enomoto, S., & Kato, T.A., 2022. Stress, Microglial Activation, and Mental Disorders. *IntechOpen, in E. Ovuga (ed.)(Stress Related Disorders)*.

Fan, T.T., Chen, W.H., Shi, L., Lin, X., Tabarak, S., Chen, S.J., Que, J.Y., Bao, Y.P., Tang, X.D., Shi, J., Sun, H.Q., & Liu, J.J., 2019. Objective Sleep Duration is Associated with Cognitive Deficits in Primary Insomnia: BDNF May Play a Role. *Sleep*, 42(1).

Fung, J., Gelaye, B., Zhong, Q.Y., Rondon, M.B., Sanchez, S.E., Barrios, Y.V., Hevner, K., Qiu, C., & Williams, M.A., 2015. Association of Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Concentrations in Early Pregnancy with Antepartum Depression. *BMC Psychiatry*, 15, pp.43.

Ghassabian, A., 2017. Determinants of Neonatal Brain Derived Neurotrophic Factor and Association with Child Development. *HHS Public Access, Dev Psychopathol,* 29(4).

Giese, M., Unternaehrer, E., Brand, S., Calabrese, P., Holsboer-Trachsler, E., & Eckert, A., 2013. The Interplay of Stress and Sleep Impacts BDNF Level. *PLoS One*, 8(10), pp.e76050.

Hardisman., 2021. *Tanya Jawab Metode Penelitian Kesehatan (1 ed.).* Yogyakarta: Gosyen Publishing.

Herba, C.M., Glover, V., Ramchandani, P.G., & Rondon, M.B., 2016. Maternal Depression and Mental Health in Early Childhood: An Examination of Underlying Mechanisms in Low-Income and Middle-Income Countries. *The Lancet Psychiatry,* 3(10), pp.983-992.

Kadic, A.S., & Kurjak, A., 2018. Cognitive Functions of the Fetus. *Ultraschall Med*, 39(2), pp.181-189.

Kemenkes., 2016. *Pedoman Pelaksanaan Stimulasi, Deteksi dan Intervensi Dini Tumbuh Kembang Anak:* Jakarta.

Kriengtuntiwong, T., Zaw, Y.H., & Taneepanichskul, N., 2021. Brain-Derived Neurotrophic Factor (BDNF) Depression and Subjective Sleep Quality in the First Trimester of Pregnancy Among Migrant Workers in Thailand. *Journal of Multidisciplinary Healthcare,* 2021.

Langgapin, S., Sirithongthaworn, S., Yang, Y., & Reddy, K.J., 2019. *Status Report on Children with Developmental Delay and Neurodevelopmental Disorders in South-East Asia*.

Lautarescu, A., Craig, M.C., & Glover, V., 2020. Prenatal Stress: Effects on Fetal and Child Brain Development. *Int Rev Neurobiol*, 150, pp.17-40.

Luo, Y., Zhang, K., Huang, M., & Qiu, C., 2022. Risk Factors for Depression and Anxiety in Pregnant Women During the COVID-19 Pandemic: Evidence from Meta-Analysis. *PLoS One,* 17(3), pp.e0265021.

McGowan, P.O., & Matthews, S.G., 2018. Prenatal Stress, Glucocorticoids, and Developmental Programming of the Stress Response. *Endocrinology*, 159(1), pp.69-82.

Miguel, P.M., Pereira, L.O., Silveira, P.P., & Meaney, M.J., 2019. Early Environmental Influences on the Development of Children's Brain Structure and Function. *Dev Med Child Neurol*, 61(10), pp.1127-1133.

Monteiro, B.C., Monteiro, S., Candida, M., Adler, N., Paes, F., Rocha, N., Nardo, A.E., Murillo-Rodriguez, E., & Machado, S., 2017. Relationship Between Brain-Derived

Neurotrofic Factor (Bdnf) and Sleep on Depression: A Critical Review. *Clin Pract Epidemiol Ment Health*, 13, pp.213-219.

Murawska-Cialowicz, E., Wiatr, M., Cialowicz, M., Gomes de Assis, G., Borowicz, W., Rocha-Rodrigues, S., Paprocka-Borowicz, M., & Marques, A., 2021. BDNF Impact on Biological Markers of Depression-Role of Physical Exercise and Training. *Int J Environ Res Public Health*, 18(14).

Olusanya, B.O., Davis, A.C., Wertlieb, D., Boo, N.-Y., Nair, M.K.C., Halpern, R., Kuper, H., Breinbauer, C., Vries, P.J.D., Gladstone, M., Halfon, N., Kancherla, V., Mulaudzi, M., kakooza, A.M., Ogbo, F.A., Olusanya, J.O., Williams, A.N., Wright, S.M., Manguerra, H., Smith, A., Echko, M., Ikeda, C., Liu, A., Millear, A., Ballesteros, K., Nichols, E., Erskine, H.E., Santomauro, D., Rankin, Z., Smith, M., Whiteford, H., Olsen, H.E., & Kassebaum, N.J., 2018. Developmental Disabilities Among Children Younger than 5 Years in 195 Countries and Territories, 1990–2016: a Systematic Analysis for the Global Burden of Disease Study 2016. *The Lancet Global Health*, 6(10), pp.e1100-e1121.

Olusanya, B.O., Hadders-Algra, M., Breinbauer, C., Williams, A.N., Newton, C.R.J., & Davis, A.C., 2021. The Conundrum of a Global Tool for Early Childhood Development to Monitor SDG Indicator 4.2.1. *The Lancet Global Health*, 9(5), pp.e586-e587.

Porcher, C., Medina, I., & Gaiarsa, J.L., 2018. Mechanism of BDNF Modulation in GABAergic Synaptic Transmission in Healthy and Disease Brains. *Front Cell Neurosci,* 12, pp.273.

Scheinost, D., Spann, M.N., McDonough, L., Peterson, B.S., & Monk, C., 2020. Associations between Different Dimensions of Prenatal Distress, Neonatal Hippocampal Connectivity, and Infant Memory. *Neuropsychopharmacology*, 45(8), pp.1272-1279.

Skogstrand, K., Hagen, C.M., Borbye-Lorenzen, N., Christiansen, M., Bybjerg-Grauholm, J., Baekvad-Hansen, M., Werge, T., Borglum, A., Mors, O., Nordentoft, M., Mortensen, P.B., & Hougaard, D.M., 2019. Reduced Neonatal Brain-Derived Neurotrophic Factor Is Associated with Autism Spectrum Disorders. *Transl Psychiatry*, 9(1), pp.252.

Sonmez, E.O., Uguz, F., Sahingoz, M., Sonmez, G., Kaya, N., Camkurt, M.A., Gokmen, Z., Basaran, M., Gezginc, K., Erdem, S.S., Dulger, H.H., & Tasyurek, E., 2019. Effect of Maternal Depression on Brain-derived Neurotrophic Factor Levels in Fetal Cord Blood. *Clin Psychopharmacol Neurosci,* 17(2), pp.308-313.

WHO., 2021. *Improving The Mental And Brain Health of Children and Adolescents*. Retrieved from https://www.who.int/activities/improving-the-mental-and-brain-health-of-children-and-adolescents.