

# The Difference of Brain Derivat Neutrophic Factor of Mus Musculus Newborn from Adolescent and Adult Pregnancy

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# The Difference of Brain Derivat Neutrophic Factor of Mus Musculus Newborn from Adolescent and Adult Pregnancy

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## Abstract

**Background:** The brain is the main organ involved in stress adaptation, while being the target of stress. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the system is adrenomedular Simpato thereby increasing the production of corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) resulting in lower levels of Brain Derived Neurotrophic Factor (BDNF) in the hippocampus. Objective: The study aims to find out the difference of BDNF of *Mus musculus* newborn brain from adolescents and adults pregnancy. Method: The samples on this study were 32 mice that divided by 2 groups were adolescent pregnancy mice group and adult pregnancy mice group. *Mus musculus* newborn were born by sectio and selected three with the heaviest, medium and lightest of each mothers to sacrificed their brains did decapitated and made immunohypochemical preparations and continued examination of the Immunoreactive Score to calculate Brain Derived Neurotrophic Factor expression. Result: BDNF expression of adolescent pregnancy mice group had higher ( $5.65 \pm 1.044$ ) than adult pregnancy mice group ( $4.15 \pm 1.049$ ). Test results showed that there was differences of BDNF expression in the brain  $p = 0,000$  ( $p < 0.05$ ) with details, there were differences in the cerebrum  $p = 0,015$  and the cerebellum  $p = 0,000$  between adolescent pregnancy mice group and adult pregnancy mice group. Conclusion: BDNF expression in brain of *Mus musculus* newborn from adolescent pregnancy lower than *Mus musculus* newborn from adult pregnancy.

**Keywords:** Stress, adolescent pregnancy, expression Brain Derived Neurotrophic Factor.

## Introduction

Adolescence is defined as the developmental phase in humans whose life cycle lies between childhood and adulthood<sup>1</sup>. According to WHO about teenage pregnancy, an estimated 16 million teenage girls give birth every year, mostly in low and middle income countries<sup>2</sup>. complications from childbirth are the main cause of death among girls between the ages of 15-19 years<sup>3</sup>. Teenage pregnancy has become an issue around the world which needs to be done to reduce the problem

of the birth of adolescent mothers<sup>4,5</sup>. Teenage pregnancy causes a serious impact on physically giving birth at an early age causing high mortality of pregnant women, triggering the emergence of problems with abortion, premature birth, preeclampsia. The psychological impact is the difficulty facing the social environment, experiencing the level of depression, difficulty in accessing to continue higher education, financial difficulties, having weak and unhealthy children<sup>6</sup>

The brain is the main organ involved in stress adaptation, as well as being the target of stress<sup>7</sup>. Stress activates the HPA axis and the adrenomedular sympathetic system thereby increasing the production of corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP). This increase because of increased secretion of adrenocorticotrophic hormone (ACTH) and glucocorticoid<sup>8</sup>.

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Brain Derived Neurotrophic Factor as the main factor that plays a role in the survival of nerve cells, as well as being involved in the proliferation, differentiation, and regulation of synapse function in the central nervous system. Acute or chronic stress affects BDNF and TrkB expression in the brain. Chronic stress decreases mRNA and BDNF protein expression in the hippocampus<sup>8</sup>.

The study aims was to find out the difference of BDNF of *Mus musculus* newborn brain from adolescents and adults Pregnancy.

### Material and Method

This was an analytic study and conducted at the Pathology Laboratory of the Faculty of Veterinary Medicine, Universitas Airlangga Surabaya which had been ethically legalized before. **Participants.** Sample size in this study were 32 samples and randomly divided into two groups. There were adolescent pregnant mice (treatment group) and adult pregnant mice (control group) Pregnant *Mus musculus* aged 1,5 months and fulfilled the criteria of study subjects for treatment group were healthy, weighing 15 – 20 grams and age 1,5 month and for control group were healthy, weighing 30-35 grams and age 3 month. *Mus musculus* that were sick or dies during treatment can't be used. **Intervention.** Each sample was given treatment according to the group which were Female mus musculus with 3 months old (Adult mice) and 1.5 months old (Adolescent mice) were impregnated with PMSG dose 5 IU and HCG dose 5 IU injections then mated with male mice aged 5 months. **Outcome.** Brain samples were taken after *Mus musculus* newborn were born then their brains were taken. For one preperat contains 3 brains sample with the heaviest, moderate and lightesst. BDNF expression

in each sample was assessed semi-quantitatively according to the modified Remmele method. Data for each sample was observed on ten fields of view (LP) at 400 x magnification. This study was examination used microscope miconos MCX50LED and camera optilab plus.

The data was carried out with comparative test using non parametric *Mann Whitney* test.

**Findings:** Pregnant *Mus musculus* randomly grouped and there were 10 mice dead from treatment group and 2 mice dead from control group. *Mus musculus* newborn had 5 mice being reabsorbtion. The Shapiro-Wilk test showed a unnormal distribution ( $p > 0.05$ ) after that using *Mann whitney* test.

**Table 1. Characteristics body weight and gestational age of *Mus musculus* mothers**

		X1		X2	
		n	%	n	%
Body weight	15-20	16	100%	-	-
	21-25	-	-	3	18,75%
	26-30	-	-	10	62,5%
	31-35	-	-	3	18,75%
Gestational Age	20 day	16	100%	16	100%

X1: Adolescent pregnancy mice (Treatment group), X2: Adult pregnancy mice (Control group)

Based on the table 1, all of K1 group samples had body weight 15-20 gram and each three samples of K2 group had body weight 21-25 gram (18,75%) and 31-35 gram (18,75%) meanwhile ten samples K2 group had body weight 26-30 gram (62,5%). All of samples group with gestational age 20 day (100%).

**Table 2: Mean body weight *Mus musculus* mothers and newborn**

Group	BW Mothers		p	BW newborn	
	Before	After		Mean±SD	p
	Mean±SD	Mean±SD			
X1	16,93±1,38	26,00±2,94	0,011	0,31±0,08	0,000
X2	28,00±2,22	41,25±5,88		0,62±0,42	

X1: Adolescent pregnancy mice (Treatment group), X2: Adult pregnancy mice (Control group)

Based on the table 2, The control group (X2) had higher mean of body weight before pregnant (28,00±2,22) than treatment group (X1) (16,93±1,38). Mean of body weight after pregnant of control group (X2) had higher mean (41,25±5,88) than treatment

group (X1) (26,00±2,94).

Mean of body weight *Mus musculus* newborn control group (X2) had higher (0,62±0,42) than treatment group (X1) (0,31±0,08).

**Table 3. Characteristics BDNF expression of Mus musculus newborn.**

Group	Cerebrum			Cerebellum			Brain		
	Mean±SD	Normality	Mann Whitney	Mean±SD	Normality	Mann Whitney	Mean±SD	Normality	Mann Whitney
X1	4,47±1,28	0,019	0,015 <sup>b</sup>	3,82±0,63	0,049	0,000 <sup>b</sup>	4,15±1,049	0,000	0,000 <sup>b</sup>
X2	5,53±1,15	0,054 <sup>a</sup>		5,76±0,95	0,033		5,65±1,044	0,007	

X1: Adolescent pregnancy mice (Treatment group), X2: Adult pregnancy mice (Control group), <sup>a</sup>: Data distribution normal (p>0,05), <sup>b</sup>: significant difference (p<0,05)

**Analysis of the results in cerebrum:** Based on table 3, mean BDNF expression of control group (X2) more high than treatment group (X1) in cerebrum. The results of the normality test showed that unnormal data distribution in treatment group (X1) (p=0,019) so we used *non parametric mann whitney test*. Table 3 shown the results that there was a significant difference of BDNF expression cerebrum between group (p=0,015).

**Analysis of the results in cerebellum:** Table 3 shown that mean BDNF expression of control group (X2) more high than treatment group (X1) in cerebellum. The results of the normality test showed that unnormal data distribution then used *non parametric mann whitney test*. there was a significant difference of BDNF expression cerebellum between groups (p=0,000).

**Analysis of the results in brain:** Based on table 3, mean BDNF expression of control group (X2) more high than treatment group (X1) in brain. The results of the normality test showed that unnormal data distribution and then used *non parametric mann whitney test*. Table 3 shown the results that there was a significant difference of BDNF expression cerebrum and cerebellum (in brain) between group (p=0,000).

## Discussion

In the adolescent group there were 10 mothers who died during treatment and 2 mothers Mus musculus in the control group who died. The gestational age of the mother mice averaged between 19-20 days, then on the 21<sup>st</sup> day a sectio caesarea was performed. Obtained adolescents pregnancy *Mus musculus* group had 3 mice abortions while the adult pregnancy *Mus musculus* group did not experience abortion. This shows that the gestational age of 1.5 months is not mature enough to reproduction function so that's difficult to get pregnant and there are many deaths issue related to stress. In accordance with the theory which shown that the age

of productive mice which ready to be impregnated is 30-40 days, this is influenced by the readiness of the reproductive organs<sup>9</sup>. The parent of juvenile mice who experience death, neither pregnancy nor abortion (reabsorption) is the impact of unpreparedness based on the age and reproductive function of mice and the mother of mice experiencing one of the three social stresses namely isolation, new environment or crowding<sup>10,11</sup>.

From the results of the study, it was also explained that there were differences of BDNF expression between Mus musculus both groups in the cerebrum, cerebellum or both (brain). In mice experiments at prepubertal levels and mid-adolescents aged 30-50 days experienced two times longer stress compared to adult aged 70 days<sup>12</sup>. Cortisol in amniotic fluid is closely related to the maternal activity of the HPA system<sup>13</sup>. The placenta enzyme 11 $\beta$ -hydroxystoid dehydrogenase-2 (HSD2) can function as an enzymatic buffer against the effects of maternal glucocorticoid exposure. However, these enzymes can reduce regulation by adverse prenatal history, which is thought to reduce the capacity to protect developing fetuses<sup>14</sup>.

Maternal depression is associated with an increase in the level of glucocorticoid mRNA receptor placenta (GR) allowing placenta GR sensitivity to be changed in stressed mothers<sup>15</sup>. Chronic stress in pregnant mice results in an evaluation of the HPA (hypothalamic pituitary Axis) by measuring plasma levels of ACTH and cortisosterone<sup>16</sup>. In experimental animals, mice undergoing pregnancy can cause differential methylation of the BDNF gene in the blood and brain<sup>16</sup>.

Stress is known to change neuronal structure during development and cause atrophy in the brain<sup>17</sup>. This can jeopardize normal hippocampal connectivity and reduce hippocampal size, reduce cognitive function<sup>18</sup> BDNF is active in the first two weeks of the mice embryo and peaks 10-14 days into the postnatal period, with the

highest levels in the hippocampus. mBDNF maintains cell survival through TrkB binding and downstream paths involving Erk1-2<sup>19</sup>. Prenatal stress changes the conventional pattern of ongoing functions. BDNF genes are clearly regulated by stress and HPA axis activation<sup>20</sup>. It is widely known that chronic stress or high glucocorticoids can reduce mRNA BDNF hippocampus expression<sup>21</sup>. BDNF signals in the hippocampus can follow one of two different signaling pathways that have opposite effects on cells, such as proBDNF, it has a high affinity for p75 receptors, which increases LTD, dendritic atrophy, and cell apoptosis. For proBDNF to be split into mature forms by plasmin, the first plasminogen zymogen must be activated by landfill. After processing, mBDNF can bind to the TrkB receptor either pre or post synaptically. In that dendrite, binding induces Erk 1/2 phosphorylation, which leads to LTP, synaptic plasticity, cell survival and differentiation

Neuroplasticity is a new hypothesis in the etiology of depression. Brain derived neurotrophic factor (BDNF) is the main neurotropic factor responsible for brain neuroplasticity and neural development. BDNF is responsible for the production, growth and differentiation of immature neurons during the stage of brain development, important for the survival of neurons. BDNF increases the development of noradrenergic and serotonergic neurons, increasing their life span by preventing them from toxic damage<sup>22</sup>. In addition, it is effective in neurogenesis and synaptic plasticity<sup>23</sup> With BDNF gene suppression, deteriorates neuroplasticity, neurons become more susceptible to pressure easily initiate apoptosis and result in atrophy<sup>23</sup>.

Hippocampus is one of the limbic structures which involves emotions and cognition. It also contributes to mood disorders such as depression, and the function of hippocambal formation and regulation of the HPA axis both change in depression<sup>24</sup>. Glucocorticoids have repeatedly been shown to reduce BDNF synthesis, which also applies to pregnancy<sup>25</sup>. Therefore, prenatal maternal HPA stress activation and fetal glucocorticoid exposure are the main mechanisms for modulating BDNF synthesis in pregnancy. Thus, prenatal maternal stress can lead to epigenetic modulation of fetal BDNF regulation, and activation of the maternal HPA system and fetal BDNF Because free diffusion is bidirectionally between the amniotic fluid and the fetus in the skin of the fetus, placenta, and umbilical cord from 10 to 20 weeks of pregnancy, the composition of amniotic fluid becomes similar to fetal plasma during this period<sup>26</sup>.

## Conclusion

BDNF expression in brain of *Mus musculus* newborn from adolescent pregnancy lower than *Mus musculus* newborn from adult pregnancy in brain.

**Conflict of Interest:** There was no conflict of interest in this study.

**Ethical Clearance:** This study was received ethical approval from the Health Research Ethics Committee, Faculty of Dental Medicine, Universitas Airlangga.

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