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The Difference Effect of Adolescent and Adult Pregnancy on Apoptosis Index of Neuron Cells

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Abstract

Context: Adolescent who are pregnant will experience depression due to physical and mental unpreparedness that affects cortisol which will reduce the secretion of Brain Derived Neurotrophic Factor, so that it will increase the index of apoptosis of brain neuron cells. This study aims to determine differences in the influence of adolescent and adult pregnancy on the index of apoptosis of brain neuron cells. The study used true laboratory experimental design with post test only control group design using animals tried to mice *Mus musculus*. The experimental group was divided into two groups: the control group or the adult pregnancy, and the treatment group or the teenage pregnancy group. The brain dissection of the newborn *Musculus* mice was taken and calculated the number of neuron cell apoptosis index using Immunohistochemical Tunnel. There were significant differences in the brain neuron cells apoptosis index with a value of $p = 0.01$ (mean $4.13 + 2.52$ in the treatment group, $2.81 + 1.43$ in the control group). There were significant differences in apoptosis index of brain neuron cells in the newborn *Mus musculus* mice in teenage pregnancy and the control group.

Keywords: *Difference, adolescent pregnancy, adult pregnancy, apoptosis index, neuron cell.*

Introduction

Pregnancy is a period starting from conception to the birth of the fetus and is a natural and physiological process, the pregnancy process is a unified chain of conception, oxidation, mother's adaptation to liquidation, maintenance of pregnancy, and hormonal changes as preparation for the baby's birth¹. World Health Organization (WHO) defines pregnancy in a girl between the ages of 10-19 years referred to as teenage pregnancy². Teenager is a period where the transition from childhood to adulthood. In adolescents who are pregnant there are complications of pregnancy that cause twice as many deaths compared with pregnancy in adult women. In addition to the causes of teen pregnancy increasing maternal mortality, pregnancy in adolescents can also cause tremendous psychological stress in these adolescents, especially in unwanted pregnancies.³ which is detrimental to the health of mother and child, is a common public health problem worldwide. It is one of

the key issues concerning reproductive health of women not only in developing countries but also in developed countries. There is growing awareness that early child bearing has multiple consequences in terms of maternal health, child health and over all well-being of the society. The purpose of the article is to review current trends and issues on adolescent pregnancy to update the practitioners. The readers are provided with more recent data on adolescent sexuality, child bearing as well as suggestions for addressing the challenges of teenage pregnancy. & lt;/p & gt; & lt;p & gt; Chatt Shi Hosp Med Coll J; Vol.15 (1 World Health Organization, recorded as many as 16 million adolescents aged between 15-19 years giving birth each year, equivalent to 11% of the total number of births in the world. As many as 59% of the total teenagers who give birth come from poor and developing countries. Pregnancy rates among adolescents in the United States are 67,8 pregnancies per 1000 women aged 15-19 years.⁴ Setting, Participants,

Interventions, and Main Outcome Measures: We used records of 38,646 women who gave birth at our hospital, between January 2008 and December 2009. Five hundred eighty-two randomly selected pregnant adolescents and 2,920 healthy parity and body mass index matched pregnant women 20-34 years of age were included the study. Perinatal outcomes were compared between the groups. Results: The mean gestational ages of the adolescent and control groups at the first prenatal visit were 11.2 (range, 8-31)⁵

Factors affecting pregnancy such as stress can affect the growth and development of the hypothalamic Pituitary Adrenal. Maternal prenatal stress is the initial environmental factor that affects cortisol reactivity in humans ^{6,7}. Unwanted pregnancies and physical and mental unpreparedness in pregnant teenage women will have an impact on mothers who will experience depression and ultimately affect fetal growth and development during pregnancy, where one of them is maternal depression which can affect the increase in neuronal cell death in the fetal brain.⁵ In the stressful condition of pregnancy, spurring an increase in the hormone cortisol through the placenta and an increase in glucocorticoids will inhibit the expression of Brain Derived Neurotrophic Factor resulting in an increase in the number of neuron cells undergoing apoptosis in the hypothalamic paraventricular nucleus ⁸. The process of apoptosis can play a role in the development of the nervous system and the final structure of brain function. Apoptosis occurs during the growth period, as a homeostatic mechanism to maintain cell populations in tissues, in reaction to cell damage.⁵

The purpose of this study was to analyze differences in the apoptotic index in adolescent and adult pregnancy in brain neuron cells.

Method

This research was experimental true laboratory research with a post test only control group design study design. The subjects of this study used experimental animals, Musculus juvenile mice aged ± 1.5 months and adult mice 3 months old obtained from the Integrated Research and Testing Laboratory (LPPT) Gajah Madah University of Yogyakarta. Mothers of adolescents and adults are given the hormone Pregnant Mare Serum Gonadotropin (PMSG) and Human Chorionic Gonadotropin (Hcg), after which mice are carried out by mating female and male mice. Pregnancy age is examined based on copulatory plug. The subjects were sacrificed and followed by sectio caesarea to give birth to Mus musculus mice and decapitation of the head and brain to dissection. The neuron cell apoptosis index is the number of neuron cells that experience apoptosis or cell death in 10 visual fields stained in the cell nucleus in the cortex area. The apoptosis index interval measurement scale was seen with a microscope 400 times magnification and calculated per 100 cells divided by the total cell number, multiplied by 1000. Using the Tunnel assay method using immunohistochemical staining examination will be stained dark brown to blackish. Apoptotic kit with the brand Santa Cruse. Data analysis using the Shapiro Wilk normality test was conducted to examine data distribution, followed by T-Test and Mann-Whitney as alternatives. Probabilities are considered statistically significant when p <0.05 is obtained with a 95% confidence interval. The data obtained is displayed in graphical form. Data analysis was processed using the SPSS version 25 (SPSS, Inc., Chicago, IL).

Results

Subjects Characteristics:

Table 1: Characteristics of Mus musculus mother based on body weight

Body weight (gram)	Control		Treatment	
	N	%	n	%
15-20	-	-	16	100
21-25	3	18,75	-	-
26-30	10	62,5	-	-
31-35	3	-	-	-
Total	16	100	16	100

The characteristics of the parent Mus musculus based on the highest body weight ranged from 15-20 grams in the treatment group (Table 5.2), ie 100% and 26-30 grams in the control group and 62.5%.

Table 2: Characteristics of Mus musculus newborn based number of children

Number of children	Control		Treatment	
	N	%	n	%
0-2	-	-	4	25
3-4	6	37,5	4	25
5-6	10	62,5	6	37,5
Total	16	100	16	100

The characteristics of the parent *Mus musculus* are based on the number of children. The majority ranged from 5-6 children in the control group (Table 5.2), which was 62.5%. All *Mus musculus* children born to the mother *Mus musculus* were weighed, then three weights were chosen, the most severe, medium, and light to be sacrificed and cut to the brain. Three brains of *Mus musculus* children were made into one preparation and immunohistochemical staining was performed and apoptosis index was calculated.

Comparison of apoptotic index in adolescent pregnancy and control group

Table 3: Mann Whitney Test Results on Apoptosis Index of brain neuron cells

Group	Apoptosis index	Mean ± S/D	Nilai p
Treatment	132,3	4,13±2,52	0,001
Control	76	2,37±1,43	

The results of the average apoptosis index in the control group were 2.37 ± 1.43 and the treatment group were 4.13 ± 2.52 . Mann whitney test Apoptosis Index of brain neuronal apoptosis index with a value of $p = 0.001$ ($p < 0.05$) which means that there is a significant difference between the control group and the treatment.

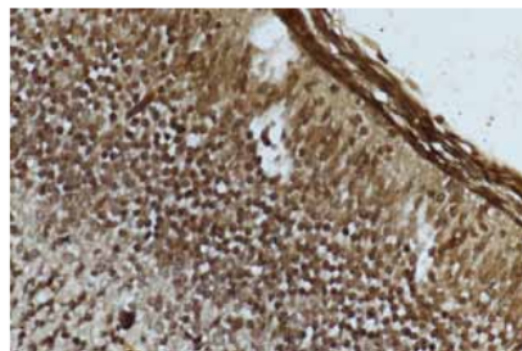
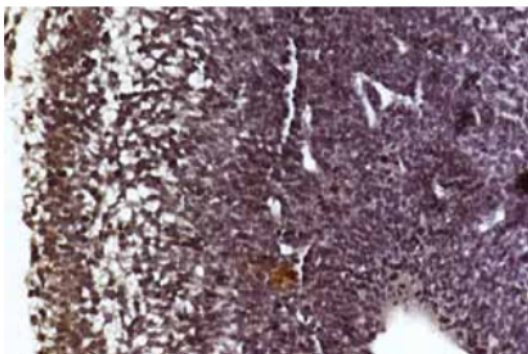


Figure 1. Microscopic test of Apoptotic Expressions. The description of expressing apoptosis in the brain is characterized by chromogen brown color (arrow) in almost all brain cells. Figure A. (Control) shows the presence of weak Apoptotic expression in the brain neuron cells of *Mus musculus* children and in Figure B. The expression of Apoptosis in brain cells is stronger than the control. 400x.

Discussion

Adolescents who are pregnant due to physical and mental unpreparedness will experience depression in these adolescents.³ which is detrimental to the health of mother and child, is a common public health problem

worldwide. It is one of the key issues concerning reproductive health of women not only in developing countries but also in developed countries. There is growing awareness that early child bearing has multiple consequences in terms of maternal health, child health

and over all well-being of the society. The purpose of the article is to review current trends and issues on adolescent pregnancy to update the practitioners. The readers are provided with more recent data on adolescent sexuality, child bearing as well as suggestions for addressing the challenges of teenage pregnancy. & It;/p & gt; & It;/p & gt;Chatt Shi Hosp Med Coll J; Vol.15 (1 The state of depression in pregnant women will cause an increase in hormones that are regulated by the hypothalamus.⁵ As with humans, in juvenile mice that are being edited also

experience stress with signs such as fear that become more aggressive, and an increase in the hormone cortisol and ultimately can cause death in these mice. In this study the juvenile mice that were edited had more deaths and were not pregnant than the control group.

In accordance with the theory which says that the age of productive mice and ready to be impregnated is the age of 8 weeks. This is likely influenced by the readiness of the reproductive organs.⁵

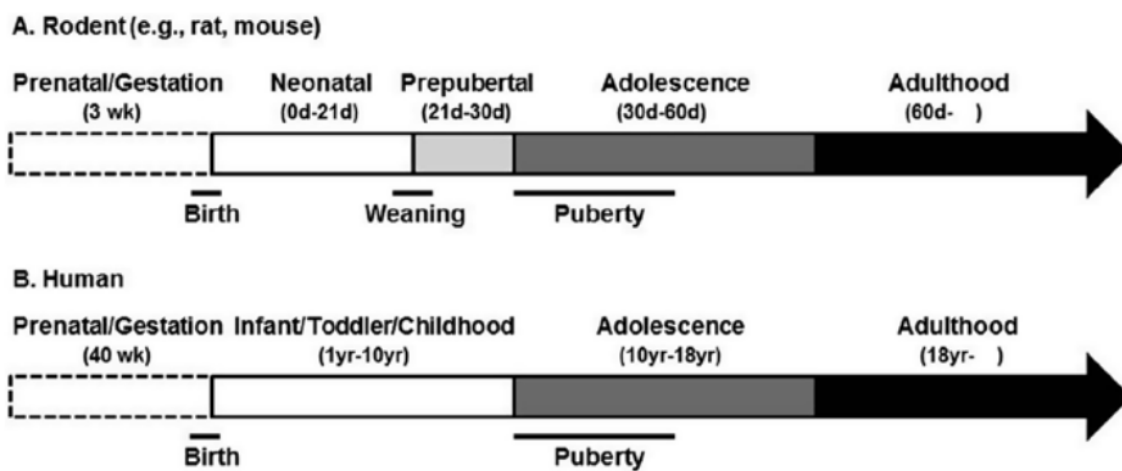


Figure 2: the growth and development of the hypothalamic Pituitary Adrenal⁹

Factors affecting pregnancy such as stress can affect the growth and development of the hypothalamic Pituitary Adrenal¹⁰. Maternal prenatal stress is the initial environmental factor that affects cortisol reactivity.⁵ Stress is referred to as a state in which the state of homeostasis in an organism is considered threatening by external or internal effects. The effector of the main end of the stress system is cortisol, which is produced by the axis of the Hypothalamic-Pituitary-Adrenal Axis (HPA Axis).¹¹

Under stressful pregnancy conditions, spurring an increase in the hormone cortisol through the placenta and an increase in glucocorticoids will inhibit the expression of Brain Derived Neutrotrophic Factor resulting in an increase in the number of neuron cells undergoing apoptosis in the hypothalamic paraventricular nucleus¹².

Path of Stress Mechanism to Neurotransmitter Signaling in Neuron Cell apoptosis

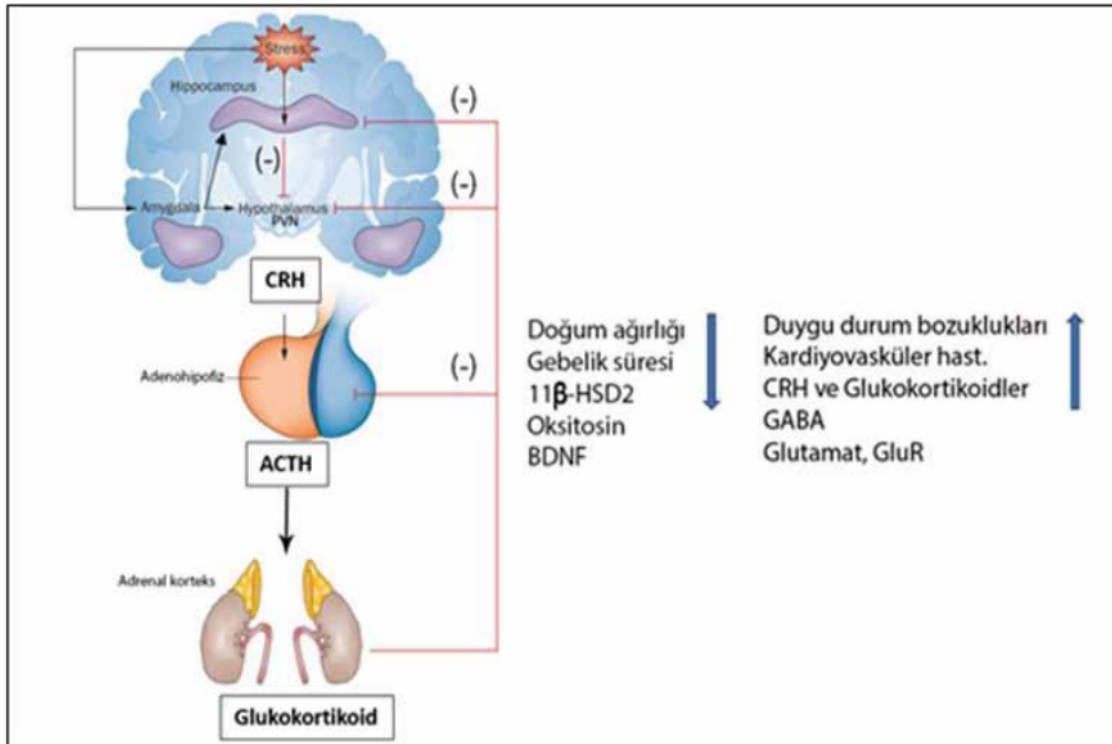


Figure 3: Mechanism of stress in pregnancy ¹¹.

During pregnancy, the hypothalamic CRH, and the placenta also produce and release CRH into the bloodstream, causing hyperactivity of the HPA axis, and a considerable increase in the ratio of free / bound cortisol. Production of placental CRH and the presence of excess cortisol begin during the second trimester and increase linearly to term, with surges in the last 6-8 weeks of pregnancy ¹³. The regulation of the prenatal HPA axis shown in Figure 2.5 has shown that when pregnant women progress, the cortisol response to acute stress reduction shows a blunt HPA axis due to high placental CRH levels. In humans, where the fetus is developing, the placenta enzyme 11β-HSD-2, which converts cortisol to cortisone is inactive, forms a maternal glucocorticoid barrier. However, 10-20% of maternal cortisol passes through the fetus, which under stress conditions is caused by increased maternal HPA activity, which gives effect to fetal cortisol and increases long-term effects on the developing brain of the fetus. ¹¹

Maternal stress and depression during pregnancy are reprogrammed ¹⁴. The HPA axis, reducing placental

enzymes 11B-HSD2 and decreasing dopamine and serotonin levels but increasing glucocorticoid / cortisol affect behavior, nerve development and signaling pathways in offspring of mice (prenatal stress models). PS exposure interferes with hippocampal neurogenesis in offspring ¹¹.

The process of apoptosis can play a role in the development of the nervous system and the final structure of brain function ¹⁵. Apoptosis occurs during the growth period, as a homeostatic mechanism to maintain cell populations in tissues, in response to cell damage ¹⁶. Pregnancy stress is associated with an increase in glucocorticoids which will inhibit the expression of Brain Derived Neurotrophic Factor (BDNF) resulting in an increase in the number of neuron cells undergoing apoptosis in the hypothalamic paraventricular nucleus *Rattus norvegicus*. ¹¹ The number of cells undergoing apoptosis depends on the synapse. The more synapses, the less apoptosis that occurs. Thus the more rich the neuron cells will dendritic site, the more synapses can be formed so that the number of cells that experience fewer

apoptosis, thus it can be concluded that brain capacity will be further enhanced¹¹.

Conclusion

From this research there are significant differences in apoptosis index of brain neuron cells in the newborn *Mus musculus* mice in teenage pregnancy and the control group. Future research is needed to prove the influence of adolescent pregnancy can have a long-term impact due to an increase in apoptosis index on structural growth, biomolecular and functional brain growth.

Conflict of Interest: None

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Ethical Clearance: Taken from The Ethics Committee of the Faculty of Dentistry, Universitas Airlangga (ethics approval number: 107/HRECC.FODM/IV/2019).

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