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Article

Differences of the Insulin and Brain Derived Neurotrophic Factor Between Normal Born Weight Baby and Baby with Intrauterine Growth Restriction.

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A B S T R A C T

Abstract

Background: Intrauterine Growth Restriction (IUGR), is a condition in which the fetal growth rate is less than 10 percentiles. Fetal growth is affected by maternal health and nutrition, the hormone insulin and placenta. Placental development is influenced by the Brain Derived Neurotropic Factor (BDNF). Insulin deficiency and BDNF can interfere with fetal development.

Method: This study used an observational research method, with a comparative cross sectional design. The place of research was conducted at Bayangkara Hospital, Dr. Rasidin, TK.III Reksodiwiryo Hospital, and Biomedical Laboratory, Faculty of Medicine, Andalas University. Research time starts from October 2017 to January 2018. The sample of this study was 25 normal babies and 25 babies with IUGR. Insulin levels and BDNF were examined by enzyme-linked immunosorbent assay (ELISA). Test the normality of the data using the Kolmogorov-Smirnov test. Statistical analysis using independent t test.

Results: Insulin levels of 13.2 ± 1.7 mIU / L in infants with normal birth weight and 8.5 ± 1.7

mIU / L in infants born with IUGR (p = 0.000) and BDNF levels 1.5 ± 0.2 ng / ml for infants with normal birth weight and 1.4 ± 0.3 ng / ml in infants born with IUGR (p = 0.008).
Conclusion Insulin levels and BDNF levels of normal birth weight babies are higher than babies born with IUGR.

I. INTRODUCTION

Intrauterin Growth Restriction (IUGR) is a condition in which fetal growth rates are less than 10 percentiles (Gaccioli and Lager, 2016; Wirakusumah, 2012). IUGR is a pathological condition where the baby's condition during the womb does not achieve maximum growth due to poor nutrition or the influence of maternal health (Sharma et al, 2016). Obstructed fetal growth will be born with a body weight of less than 2500 grams or an estimated fetal weight <10 percentile of the normal weight curve. In addition, small babies during pregnancy (KMK) also called Small for Gestational Age (SGA) are low birth weight but in accordance with the age of pregnancy (Gaccioli and Lager, 2016). Fetal growth is influenced by several factors such as genetic, maternal health and nutrition, availability of growth substrates, placenta, brain derived neurotrophic factor (BDNF), and insulin hormones (Mayeur et al, 2010; Sharma et al, 2016).

Insulin functions to send glucose to the embryo and fetal growth (Blackburn, 2013). Glucose is the main nutrient needed for the fetus and placenta. Placental glucose uptake and transport to the fetus occur in the maternal circulation to the fetus that crosses the placenta (Sherwood. 2011; Zhang et al, 2015).

Brain Derived Neurotrophic Factor (BDNF) is a part of the family of neurotrophin, including in the neurotrophic factor found in mammals. BDNF is widely expressed in the Central Nervous System (CNS), hypothalamus, hippocampus and brain. This neurotrophin affects almost all aspects of CNS development in the fetus, and after birth (Mayeur et al, 2010). BDNF and neurotrophin-4 (known as neurotrophin-4/5) are also secreted by ovarian and uterine epithelial cells. In the development of blastocysts, the role of paracrine is also autocrine BDNF and NT-4/5, during embryonic development, implantation and placentation processes (Christian et al, 2016). Placental development is important for fetal growth and pregnancy. The main determinant of fetal growth is the supply of placental nutrition, and this process depends on size, morphology, blood flow, and placental transport (Mayeur et al, 2010; Zhang et al,

2015). In fetuses who experience growth inhibition of mothers who are malnourished, will experience a reduction in BDNF which will increase placental apoptosis (Mayeur et al, 2010).

The placenta is the main organ between the fetus and mother that plays an important role in maintaining fetal development and growth and as a substrate transporter (Zhang et al, 2015). The main substrates needed for fetal growth include oxygen, glucose, amino acids, fatty acids, and the process of transferring them depending on the characteristics of the placenta, such as placental size, shape, and circulation of the placenta (Cunningham et al, 2013; Zhang et al, 2015).

Placental development is strongly influenced by several hormones like insulin and Brain-derived Neurotrophic Factor (BDNF), (Christian et al, 2016) besides BDNF also functions important during pregnancy, due to follicular development, implantation, and placentation in uterine tissue (Mayeur et al, 2010).

Deficiency or excess growth and nutrition of the fetus can affect the function and amount of adipose tissue, will have long-term effects on the baby that is impaired neurological development, increased child mortality, and the tendency of chronic diseases such as hypertension, coronary artery disease, and type 1 diabetes or type 2 diabetes in later adulthood (Mayeur, 2010; Blackburn, 2013).

METHODS

The study was observational with a comparative cross sectional design. The study was conducted in RSUD dr. Rasidin Padang, Third Level Reksodiwiryo Padang Hospital, Padang Bayangkara Hospital, and the Biomedical Laboratory of the Faculty of Medicine, Andalas University, from November 2017 to January 2018 after passing the research ethics test from the Faculty of Medicine, Andalas University (Number 391 / KEP / FK / 2017). The sample in this study consisted of 2 groups: 25 newborns with normal weight and 25 newborns with IUGR, sample collection using Consecutive Sampling techniques.

The population in this study were newborns with term at gestational age who were born in RSUD dr. Rasidin Padang, Tk III Reksodiwiryo Padang Hospital, Padang Bayangkara Hospital. Inclusion writers in this study are mothers who are willing to become respondens and sign infomed consent, mothers with a single pregnancy, live fetuses.

After signing informed consent, anthropometric measurements were taken, and umbilical cord blood sampling was ± 3ml by the researcher. Then the serum sample was sent to the Biomedical Laboratory of the Andalas University

Medical School using a cooler bag to be stored in the refrigerator with a temperature of -20 ° C. Serum measurements are performed after all samples have been collected. Then the insulin level and BDNF were examined by the ELISA method. Normality test using Kolmogorov-Smirnov Test (number of samples = 50). Bivariate analysis uses an independent t test with a value of p <0.05.

RESULT

Characteristics of research respondents can be seen in table 1 which shows that there is a significant relationship between placental weight in normal infants and the Intrauterine Growth Restriction (IUGR) p <0.01. Table 2 shows that there are significant differences where normal babies insulin levels are higher than IUGR (p <0.01). Table 3 shows that there are significant differences in normal BDNF levels of infants higher than IUGR (p <0.008).

Table 1: Characteristics of study respondents based on placental weight..

Karakteristik		Bayi Normal n = 25		Bayi *IUGR* n = 25		*p*
		f	%	f	%	
Berat plasenta	Normal	25	100	2	4	0,001
	Tidak Normal	0	0	23	46	
Total		25	100	25	100	

Table 2: Differences in insulin levels between normal birth weight babies and babies born with IUGR.

Variabel	n	Bayi normal Rerata ± SD	Bayi IUGR Rerata ± SD	*p*
Kadar Insulin mIU/L	25	13,16 ± 1,66	8,53± 1,71	0,001

Tabel 3 : Perbedaan kadar *BDNF* pada bayi berat lahir normal dan bayi lahir dengan *IUGR*.

Variabel	n	Bayi normal Rerata ± SD	Bayi IUGR Rerata ± SD	*p*

DISCUSSION

Low Birth Weight (LBW) is one of the main causes of high infant mortality. Low birth weight is usually caused by inhibition of fetal growth or Intrauterine Growth Retriction (IUGR).

Intrauterine Growth Restriction (IUGR), is a condition in which the fetal growth rate is less than 10 percentile. Fetal growth is affected by maternal health and nutrition, insulin hormone and placenta. Placental development is influenced by the Brain Derived Neurotropic Factor (BDNF). Insulin deficiency and BDNF can interfere with fetal development.

Thus the authors are very interested in conducting research on differences in insulin levels and Brain-Derived Neurotrophic Factor (BDNF) between normal babies and Intrauterine Growth Retriction (IUGR).

Based on this study there is a significant relationship between the weight of the placenta and the weight of the baby born. Normal fetal growth is characterized by the weight gain of the placenta in line with fetal weight gain (Kosim, MS. Et al., 2010). Thin and brittle placenta is usually found in newborns with low weight and will experience a failure in the supply of nutrients from mother to fetus. Placental failure to provide adequate nutrition to the fetus is called placental insufficiency and will result in intrauterine growth retriction (IUGR) (Saifuddin, AB. 2014; Sharma et al 2016).

The results of this study were 27 (54%) placenta of babies with normal weight of ≥500 grams and 23 (46%) placenta weighing ≤500 grams. The results of statistical tests ($p < 0.01$) showed a significant relationship between the weight of the placenta and the baby's birth weight.

The placenta is a fetal organ located between the fetus and mother and plays an important role in fetal development and growth by facilitating the transfer of substrate from mother to fetus (Zhang et al, 2015). The main substrate needed for fetal growth are oxygen, glucose, amino acids and fatty acids, and their transport process depends on the characteristics of the placenta, such as placental size, morphology, blood flow and vascularization (Mayeur et al, 2010; Zhang et al, 2015) Thin and brittle placenta is usually found in newborns with low weight (Saifuddin, AB. 2014; Sharma et al 2016). Small and fragile placenta will fail in the supply of nutrients from mother to fetus. Placental failure to provide adequate nutrition to the fetus is called placental insufficiency and will result in intrauterine growth retriction (IUGR) (Zhang et al, 2015).

The results of this study are in line with research conducted by Pati, AA. et al., (2012) 11, it was found that the mean placental weight was 590 ± 82 grams, and the mean infant birth weight was 3275 ± 469 grams, with the results of the statistical test $p < 0.05$ which means that there was a significant relationship between the weight of the placenta and birth weight baby. Placental development is strongly influenced by several hormones are insulin and Brain-derived Neurotrophic Factor (BDNF), (Christian et al, 2016).

The results of this study found that insulin levels of normal babies were higher than IUGR, which was 13.16 ± 1.66 mIU / L in normal infants and 8.53 ± 1.71 mIU / L in IUGR, $p < 0.01$.

According to Lee et al., (2016) The results of insulin levels in normal infants were 5.6 ± 6.1ng / ml, higher compared to insulin levels of IUGR infants 2.8 ± 1.1ng / ml, $p = 0.01$. Fetal growth is influenced by nutritional, endocrinological and placental

factors. Glucose is known as the main substrate of fetal metabolism and insulin plays a role in fetal growth. Insulin stimulates cell growth and stimulates cell proliferation, therefore fetal hypoinsulin affects soft tissue growth and causes IUGR.

Research by Pardo et al., (2004) insulin levels of newborns ranged (9,71-10,79) mIU / L. When compared with the results in this study insulin levels in normal infants are higher, namely 13.16 ± 1.66 (11.5-14.82) mIU / L. The difference in this study with the research of Pardo et al., (2004) is likely due to differences in characteristics and research samples. Where in this study were not separated between the sex of the baby, maternal nutritional intake during pregnancy, glucose tolerance test at 24 to 26 weeks of pregnancy, type of labor and differences in measuring instruments for insulin testing. In the Pardo study insulin testing used radioimmuno assay.

The results of this study normal BDNF levels of infants were higher than IUGR, which was 1.58 ± 0.23 ng / ml in normal babies, and 1.37 ± 0.3 ng / ml in IUGR with p = 0.008 where p <0 , 05.

Afify et al., (2005) study 1 in 80 newborns divided into 3 groups: group 1 (n = 24) gestational age 24-30 weeks, group 2 (n = 34) gestational age 31-36 weeks, and group 3 (n = 22) gestational age of 37-42 weeks. There were significant differences in BDNF levels between groups 1 and 2 (p = 0.0002), groups 2 and 3 (p = 0.0001), and groups 1 and 3 (p = 0.0001).

BDNF levels increase with increasing gestational age along with fetal brain development. This is contrary to the research of Malamitsi-Puchner et al., (2006) which in his study of 30 neonates stated that there are no significant difference in BDNF levels between term neonates and IUGR. In fetuses experiencing growth retardation is often associated with malnutrition and hypoxia, so the fetus adapts to distribute blood flow to important organs such as the brain, heart and adrenal glands, at the expense of other organs such as the kidneys. So that there is no difference in BDNF levels between normal neonates and IUGR.

According to Christian, (2016) which states that low serum BDNF levels at the end of pregnancy can result in a low risk of a baby being born. This is because BDNF and its receptor TrkB have the potential to develop placenta and fetal growth from mid pregnancy until the end of pregnancy (Mayeur et al., 2010). This study was supported by Dhobale et al., (2013) which was carried out in 38 term infants (> 37 weeks) and 37 preterm infants (<37 weeks) p = 0.031 concluded that BDNF levels were lower in preterm infants compared to term infants. And there is a positive relationship between BDNF, placenta, infant weight,

head circumference, and chest circumference, which indicates that BDNF plays a role in fetal growth and development.

According to Uguz, et al, (2013) BDNF levels in normal babies were lower than the normal limit of 2.08 ± 0.91 ng / ml taken from the study. Possible due to anxiety in the mother during labor. BDNF levels are lower in infants whose mothers experience anxiety disorders (Uguz, et al, 2013). Low BDNF levels will affect neural development and infant brain development.

BDNF levels in the umbilical cord are affected by baby's sex, kind of delivery (vaginal delivery or surgery through sectio caesarea), and cortisol hormone. Flok et al 2016 found a constant increase in BDNF levels in newborns after vaginal delivery and low levels of BDNF in infants born through cesarean section, but the molecular underlying these findings has not been explained further. Development of the placenta is very important for fetal growth. Low placental weight is often associated with fetal growth restriction of maternal hypertension and preeclampsia. The main determinant of fetal growth is the availability of nutrients and this process depends on size, blood flow, and placental transport (Mayeur et al., 2010; Lee et al., 2016).

CONCLUSION

There are significant differences in which insulin levels of normal born babies are higher than babies born with IUGR.

There are significant differences where BDNF levels of normal born babies are higher than babies born with IUGR.

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