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Differences in Brain-Derived Neurotrophic Factor and Matrix Metalloproteinase-9 between Appropriate Neonates between Normal Birth Weight and Intrauterine Growth Restriction

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Abstract

BACKGROUND: Intrauterine Growth Restriction (IUGR) was defined as the growth of the fetus less than its normal potential growth due to genetic and environmental factors. One of the most widely believed causes of IUGR was impaired uteroplacental mechanism from mother to fetus. Furthermore, factor which was thought to affect placental growth was due to the influence of Brain-Derived Neurotrophic Factor (BDNF) and Matrix Metalloproteinase (MMP-9) which play an important role in angiogenesis.

AIM: This study aims to determine differences in Brain-Derived Neurotrophic Factor (BDNF) and moderately mature Matrix Metalloproteinase (MMP-9) between normal birth weight and intrauterine growth restriction.

MATERIAL AND METHODS: The study design was a cross-sectional study at four hospitals in Padang city from August 2017-January 2018. The sample of this study was umbilical cord blood of appropriate gestational age neonate with normal birth weight (31 neonates) and IUGR (31 neonates) by consecutive sampling, samples taken from mothers who meet inclusion criteria. BDNF and MMP-9 levels were analysed by ELISA. The differences between normal birth weight and IUGR test were followed by unpaired T-test.

RESULTS: The results showed that BDNF levels in normal neonates was 1.58 ± 0.23 ng/ml and in IUGR neonates were 1.25 ± 0.35 ng/ml (p = 0.001). MMP-9 levels in normal neonates was 1.09 ± 0.20 ng/ml and in IUGR neonates were 1.25 ± 0.35 (p = 0.03).

CONCLUSION: The conclusion of this study was BDNF of moderately mature neonates was significantly higher in normal birth weight compared to intrauterine growth restriction, and the moderately high MMP-9 neonates were significantly higher in intrauterine growth restriction compared with normal birth weight.

Introduction

IUGR is defined as fetal growth that is less than normal potential growth due to genetic and environmental factors. IUGR is included in the category of low birth weight babies (LBW) [1]. IUGR is assessed by looking at the baby's growth chart. IUGR was diagnosed when the baby was born with a low birth weight (below the 10th percentile) with clinical signs of malnutrition [2]. If intrauterine growth disorders occur early in the pregnancy, it will have an impact on the growth of the brain and skeletons which are disrupted by the result associated with poor nerve development [3].

IUGR affects around 24% of newborns where around 30 million babies worldwide suffer from IUGR each year. One third (75%) occurs in Asia; the rest occurs in Africa (20%) and Latin America (5%). Indonesia ranks fourth for IUGR cases from all countries in Asia after Sri Lanka, Cambodia and Vietnam [2]. The cause of IUGR tends to be due to a disruption of the uteroplacental mechanism from mother to fetus. The placenta is an organ that facilitates the exchange of gas and nutrients between mother and fetus. If there are abnormalities in the placenta, this exchange will be disrupted; the fetus will not get enough nutrients needed to grow which will eventually lead to IUGR [4].

One of the factors thought to influence the

process of placental growth is due to the influence of Brain-Derived Neurotrophic Factor (BDNF) and Matrix Metalloproteinase (MMP-9). In a study showed that there were differences in BDNF levels in the placenta in pregnant women with preeclampsia where a higher BDNF level was found in patients with normotensive [5]. in another study found that the absence of MMP-9 in mice can cause severe abnormalities and lack of MMP-9 which causes disruption of trophoblast differentiation and the occurrence of defects in maternal blood vessels [6].

BDNF is one of the proteins needed for the growth of neurons. During the development period, BDNF plays a role in nerve growth, differentiation, repair, and survival of nerve cells [7]. Also, BDNF also shows an important role during the implantation period, placental development and fetal growth development in mice [8]. BDNF is known to have an important role in regulating angiogenesis needed for placental development [9]. Because of this role, BDNF deficiency will disrupt placental growth which in turn will cause fetal growth disorders or intrauterine growth restriction (IUGR) [8].

There are several factors that affect BDNF levels, including age, sex, weight, iron deficiency anaemia and depression. BDNF is inversely proportional to age and weight. Getting older and getting heavier, the BDNF decreases. Research showed that respondents aged 20-33 years have BDNF higher than respondents aged > 34 years. Women also tend to have low BDNF compared to men. Depressed pregnant women also have low BDNF concentrations [10], [11]. The umbilical cord BDNF levels are also influenced by maternal ferritin, where levels tend to be lower in women with iron-deficiency anaemia (< 12 ng/ml) than mothers with normal ferritin levels (≥ 12 ng/mL) [12].

Besides BDNF, another factor that affects placental growth is Matrix Metalloproteinase-9 (MMP-9). MMP-9 is believed to facilitate trophoblast invasion with its role as the destroyer of the extracellular matrix in the process of placentation. MMP is known as a mediator in tissue remodelling and angiogenesis. If this process is interrupted, the trophoblast will not be embedded properly in the uterus. As a result, the distribution of nutrients to the fetus will also be disrupted which will eventually lead to IUGR.

Based on the description above, the researcher wanted to conduct a study on the differences in Brain-Derived Neurotrophic Factor (BDNF) and the moderately mature Matrix Metalloproteinase (MMP-9) between normal birth weight and intrauterine growth restriction. This research is important to do with the hope that BDNF and MMP-9 placenta can be used as predictors to assess the occurrence of IUGR in pregnancy. The study was conducted in several hospitals in the city of Padang.

Material and Methods

This study was an observational study with cross-sectional [13]. This research was conducted from August 2017 to January 2018 at four hospitals in the city of Padang. Examination of BDNF and MMP-9 levels was carried out at the Biomedical Laboratory, Andalas University, Padang.

Population and Sample

The population in this study was all month-old neonates who were admitted to several hospitals in Padang city at the time of the study. The inclusion criteria in this study were those who were willing to be the subjects of the study, the age of mothers 20-33 years old, can remember HPHT or can show the results of TMG ultrasound examination 1, did not suffer from anemia (Hb11 gr/dl) and did not experience depression assessed from the questionnaire EPDS (Edinburgh Postnatal Depression Scale) (score > 13). Exclusion criteria are mothers with leukocytes > 13,000 mm^3 and blood glucose when > 200 mg/dl.

A total of 62 respondents as the study sample were taken using non-probability sampling methods by consecutive sampling. All subjects who came in sequence and fulfilled the inclusion criteria were included in the study until the required number of subjects was fulfilled [13].

Data normality test is done by using the Shapiro Wilk test. Data distribution is said to be normal if the significance value (sig) > 0.05). Data normality test was conducted to determine whether the data distribution of each variable. Data that is normally distributed is calculated on average and standard deviation. Bivariate analysis is used to determine the relationship between two variables. If it is normally distributed the unpaired t-test is used.

How to take samples

The method of sampling in this study is non-probability sampling that is by card consecutive sampling. All subjects who arrived sequentially and fulfilled the inclusion criteria were included in the study until the number of subjects needed was met [13].

How to determine sample size

Use the comparative numerical-numerical Lemeshow formula of two independent groups:

Sample formula

$$\mathrm{n}_1 = n_2 = 2\left(\frac{[\mathrm{Z}_\alpha + \mathrm{Z}_\beta]\mathrm{s}}{\mathrm{x}_1 - \mathrm{x}_2}\right)^2$$

n = Sample size, Zα = Error type 1 (α) of 5% = 1.96, Zβ = Error type 2 (β) of 10% = 1.28, S = Combined standard deviation, (x1-x2) = the smallest difference clinically important (Determined by researchers).

Because there are two variables examined by the researcher, then each sample size of the two variables will be searched for later compared to which sample size is greater.

a. BDNF

The standard deviation of the two groups is obtained based on the following calculations [14]:

$$(\mathrm{Sgab})^2 = \frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}$$

Sgab = Combined standard deviation

S1 = Standard deviation of group 1 = 3.153

n1 = Sample size of group 1 = 12

S2 = Standard deviation of group 2 = 1.718

n2 = Amount of sample group 2 = 34

Based on the formula above, the combined deviation is obtained as follows:

$$(\mathrm{Sgab})^2 = \frac{13.153^2\ (12 - 1) + 1.718^2\ (34 - 1)}{12 + 34 - 2}$$

Based on the formula above, the number of subjects is as follows:

$$n_1 = n_2 = 2\left(\frac{[1{,}96 + 01{,}28]2.167{,}72}{1.879}\right)^2 = 27{,}82 = 28$$

b. MMP-9

The standard deviation of the two groups is obtained based on the following calculations [15]:

$$(\mathrm{Sgab})^2 = \frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}$$

Sgab = Combined standard deviation, S1 = Standard deviation of group 1 = 87.4, n1 = Sample size of group 1 = 24, S2 = Standard deviation of group 2 = 53.37, n2 = Amount of sample group 2 = 38.

Based on the formula above, the combined deviation is obtained as follows:

$$(\mathrm{Sgab})^2 = \frac{87{,}4^2\ (24 - 1) + 53{,}37^2\ (38 - 1)}{24 + 38 - 2}$$

$$\mathrm{Sgab} = \sqrt{4.684{,}69} = 68{,}44$$

Based on the formula above, the number of subjects is as follows:

$$n_1 = n_2 = 2\left(\frac{[1{,}96 + 0{,}842]68{,}44}{104{,}5}\right)^2 = 8{,}48$$

Based on the calculation of the sample size of the two variables, the largest number of samples was taken, amounting to 28 people. To anticipate the subject who dropped out, the calculation was carried out as follows:

$$\boldsymbol{n = \frac{n}{1 - f}}$$

$$\boldsymbol{n = \frac{28}{1 - 0{,}1}}$$

$n = 31{,}1 = 31$, n = sample size = 28, f = estimated proportion of drop out = 10% = 0.1.

After anticipating the drop-out subjects, the sample size was 32, so that the total sample taken was 62 people (31 enough months with IUGR and 31 moderately-term neonates with normal birth weight).

Taking Blood Serum

Taking 3 ml umbilical cord blood sample using 3 ml syringe conducted by officers and researchers. The blood taken is taken by the researcher into a centrifuge tube (vacutainer) without anticoagulation using the syringe handle which is allowed to bleed itself from the syringe tube. Blood in the vacutainer is placed on the tube rack to avoid shocks and remain in position. The blood is allowed to stand for 15-20 minutes then centrifuged within 30 minutes at 3000 rpm for 10 minutes. Blood that has been centrifuged and then taken by the serum using a micropipette is then inserted into the 1½ ml cup serum that has been coded according to the identity of the respondent. Blood samples that have hemolysis are removed. The sample serum is then put into the refrigerator at a temperature of 40-60°C (a maximum of 24 hours) and then sent to the Biomedical laboratory, Faculty of Medicine of the Andalas University using a cool box containing ice gel (which has been frozen for at least 24 hours at -18°C) in time 4 hours. Deliveries will be made during laboratory working hours, namely at 08.00-16.00 WIB. Then the serum is stored in the refrigerator -80°C until the examination is done. After all the serum is fulfilled, then BDNF levels are examined using the Human BDNF ELISA Kit and MMP-9 levels using the Human MMP-9 ELISA Kit at the Biomedical Laboratory of the Faculty of Medicine, Andalas University.

***Examination of BDNF Levels* (*Work protocol based on Human BDNF ELISA Kit*)**

All reagents, samples and standards are prepared according to the instructions. All reagents and samples were left at room temperature 18-25°C before use. After that, 100 µL standard or sample is

added to each well then incubated for 2,5 hours at room temperature or overnight at 4°C. Then the prepared Streptavidin solution is then added to it for 45 minutes at room temperature. After that 100 µL of TMB One-Step Substrate Reagent was added to each well then incubated for 30 minutes at room temperature. Finally added 50 µL Stop Solution at each well then read immediately with a wavelength of 450 nm. Obtained the concentration value of the sample examined.

Examination of MMP-9 Levels (*Work protocol based on the Human MMP-9 ELISA* Kit)

All reagents, samples and standards are prepared according to the instructions. All reagents and samples were left at room temperature 18-25°C before use. After that, 100 µL standard or sample is added to each well then incubated for 2.5 hours at room temperature or overnight at 4°C. Then the prepared Streptavidin solution is then added to it for 45 minutes at room temperature. After that 100 µL of TMB One-Step Substrate Reagent was added to each well then incubated for 30 minutes at room temperature. Finally added 50 µL Stop Solution at each well then read immediately with a wavelength of 450 nm. Obtained the concentration value of the sample examined.

Data analysis

The data normality test was carried out using the Kolmogorov Smirovov test (sample ≥ 50). Data distribution is said to be normal if the significance value (sig) > 0.05, and if sig < 0.05, the data is not normally distributed. Data normality test was conducted to determine whether the data distribution of each variable. Data that is normally distributed is calculated on average and standard deviation. Data is abnormally distributed, calculated median values and maximum minimums. Categorical data is calculated by frequency distribution.

Research Ethics

This research has received ethical considerations and approval from the Research Ethics Committee Team Faculty of Medicine of Andalas University with registration number 236/KEP/FK/2017.

Results

The normality test was carried out in groups using the Shapiro Wilk test. The test results in Table 1 show that data are normally distributed (p > 0.05). Data with normal distribution will show the mean value. Then a comparative test of 2 unpaired groups was then carried out.

Table 1: The characteristics of the research subject

Characteristics	Normal	IUGR	P value
Age of mother (year)	27 (2-33)[b]	28 (20-33)[b]	0.86
IMT	22.61 ± 1.89[a]	22.05 ± 1.86[a]	0.25
Hb level (g/dl)	11 (11-12.6) [b]	11 (11-12.7) [b]	0.98
Level of GDS (g/dl)	93.52 ± 10.16[a]	94.65 ± 14.11[a]	0.72
Leukocytes (/mm^3)	9720.32 ± 1793.83[a]	10137.74 ± 19.09.06 [a]	0.38

It can be seen that there is not one variable that has a significant difference in the two groups. This means that the characteristics of the two groups considered being homogeneous.

Differences in BDNF Levels in Normal Babies and IUGR

In the initial process of testing normal data distribution, the BDNF level shows normal data distribution which can be seen in Table 2. Therefore the data displayed is average. Table 2 shows that there are differences in BDNF levels between normal infants with IUGR.

Table 2: BDNF levels for each group of research subjects

	N	BDNF Levels (ng/mL)		*P value*
		Mean	SD	
Normal	31	1.58	0.23	0.001*
IUGR	31	1.25	0.35	

* p < 0.05. Independent t-test.

Differences in MMP-9 Levels in Normal Babies and IUGR

In the initial process of testing the distribution of normal data, MMP-9 levels show normal data distribution which can be seen in Table 3. Therefore the data displayed is in the form of a mean.

Table 3: MMP-9 levels for each group of research subjects

	N	MMP-9 Levels (ng/mL)		*P value*
		Mean	SD	
Normal	31	1.09	0.20	0.03*
IUGR	31	1.25	0.35	

* p < 0.05. Independent t-test.

Table 3 above shows that there are differences in MMP-9 levels between normal infants with IUGR.

Discussion

Differences in BDNF Levels in Normal Babies and IUGR

There were significant differences between the median BDNF levels in normal infants, which were 1.58 ± 0.23 ng/ml and BDNF levels in IUGR infants

were 1.25 ± 0.35 ng/ml which can be seen in Table 2.

Previous studies have shown that a decrease in serum BDNF at the end of pregnancy is associated with a risk of low birth weight [16]. Also, other studies have also found the role of BDNF in energy angiogenesis and homeostasis in the uteroplacental system which allows in influencing the aetiology associated with impaired placental growth and the fetus including one of them IUGR [8].

One of the most studied neurotrophin members is BDNF. Several studies have highlighted the critical role of neurotrophin in particular NGF and BDNF during pregnancy [14]. BDNF has been reported to have a role in embryo implantation, placental development, fetal growth from mid-gestational to advanced gestation by increasing trophoblast cell growth and survival in mice suggesting a possible role in the development of fetoplacental units [17].

In the study stated that one of the forms of neurotrophin is BDNF, a molecule that regulates placental and brain development. Placental development is very important during pregnancy because it forms the interface between the maternal-fetal circulation and is essential for fetal nutrition and oxygenation. Also, BDNF also tends to influence the birth and development of neurons through two mechanisms, namely angiogenesis and cell growth, defence and maturation [18].

However, in other studies, there were no significant differences in BNDF levels when observed between term infants with IUGR and term infants with normal birth weight (AGA/Age of Proper Pregnancy) measured from the mother, fetus, and neonatal side. This result may be due to differences in the characteristics of the sample under study where more criteria are used in determining the sample to be taken. These criteria include the presence or absence of polyhydramnios, congenital infections, and chromosome assessment for mothers over 35 years to assess the risk of fetal anomalies. Also, the assessment of smoking behaviour and drinking habits is also assessed. This study also included mothers with severe anaemia and diabetes while both were exclusion criteria in this study [19].

Differences in MMP-9 Levels between Normal Babies and IUGR

There is a difference between MMP-9 levels in normal infants which is 1.09 ± 0.20 ng/ml and the mean MMP-9 level in IUGR infants is 1.25 ± 0.35 ng/ml which can be seen in Table 3.

In line with the research conducted who found that placentas from pregnancies with IUGR showed a decrease in the release of MMP-2, MMP-9 and TIMP-1 compared to normal pregnancies [20]. Other studies also found that a decrease in MMP-9 levels affected the pathological processes underlying the occurrence of preeclampsia and IUGR in both preeclampsias and normal pregnancies with IUGR [21]. Different results were found in other studies that MMP-9 levels had no significant relationship with gestational age and infant birth weight. These different results may be due to using premature infants as respondents while this study assessed fairly month's infants [22].

Matrix metalloproteinases (MMPs) are members of the protease family that can degrade extracellular matrix (ECM) and connective tissue proteins [23]. MPMP-9 is expressed by the uterus and plays a role in remodelling uterine tissue in the estrus cycle, menstrual cycle and pregnancy in both animals and humans. MMP-9 has also been found to increase in the myometrium and aorta of pregnant mice which shows its role in the uterus and vascular remodelling MMP-9 also plays a role in angiogenesis by allowing endothelial cells to escape and move into new tissues and also by releasing proangiogenic factor matrix [24].

MMPs are families of zinc-dependent endopeptidases that divide the ECM component and are involved in embryo implantation, placental development and also in the process of labour. Research shows that the development of the maternal-fetal circulation and the success of pregnancy in humans require the invasion of trophoblast cells into the endometrial stroma and the lining in all three myometria. This invasion ability is mediated by MMPs where the most important role is held by MMP-9 [5].

Deficiency of MMP-9 can disrupt trophoblast invasion and will lead to abnormal and superficially implanted placenta as in preeclampsia. Low MMP-9 levels are found in patients with preeclampsia and cases of IUGR [5]. Experiments in pregnant rats proved that placentas that did not have MMP-9 showed smaller implantation spaces and embryos with a significantly reduced body weight that matched the characteristics of IUGR [6].

In this study only assessing IUGR, not classifying whether symmetrical or asymmetrical. This research can use to determine the aetiology and pathophysiology of IUGR by looking at BDNF and MMP-9 levels and as a preventive measure in preventing the occurrence of IUGR in pregnant women by avoiding the risk factors for low BDNF levels, namely age (< 20 or > 33 years), iron deficiency anemia (Hb < 11gr /dl), and avoiding depression as assessed from the EPDS questionnaire (Edinburgh postnatal depression scale) (score < 13). In a cross-sectional study, IUGR can be diagnosed if the neonatal body weight is below the 10th percentile based on the Lubchenco growth curve. Pretty month neonates who were born at 37 to 42 weeks' gestation were weighed within < 24 hours.

In conclusion, BDNF of moderately mature neonates was significantly higher in normal birth weight compared to intrauterine growth restriction and

the moderately high MMP-9 neonates were significantly higher in intrauterine growth restriction compared with normal birth weight.

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