DEXAMETHASONE STUDY FOR PRENATAL LUNG MATURATION ON LECITHIN/SPHINGOMYELIN RATIO IN WOMEN AT RISK OF PRETERM BIRTH

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ABSTRAK

*Betametason dan deksametason adalah antenatal kortikosteroid yang digunakan dalam penurunan RDS (respiratory distress syndrome), penyebab tersering prematuritas pada bayi. RDS terkait dengan imaturitas struktur dan fungsi paru yang ditentukan dengan rasio lesitin/sfingomielin (L/S) sebagai gold standard. Sampai saat ini belum ada penelitian yang membandingkan deksametason dengan regimentasi berbeda. Penelitian ini dilakukan untuk menganalisis penggunaan deksametason dengan dosis lebih rendah dalam mempercepat maturitas paru janin. Penelitian ini bertujuan mengkaji penggunaan deksametason dosis 4 mg dan 6 mg setiap 12 jam selama 2 hari pada ibu hamil, dengan resiko kelahiran preterm terhadap nilai rasio L/S sebagai parameter maturitas paru janin. Jenis penelitian ini adalah longitudinal prospektif dengan dua kelompok perlakuan yaitu kelompok deksametason 4 mg dan deksametason 6 mg yang diberikan secara IM setiap 12 jam selama 2 hari. Besar sampel sebanyak 34. Sampel penelitian adalah cairan ketuban ibu hamil beresiko persalinan preterm dengan usia kehamilan 28-34 minggu. Penetapan rasio L/S dilakukan dengan metode ELISA. Penelitian dilakukan pada Juli 2013-Januari 2014 dan mendapatkan izin kelaikan etik dari RSUD Dr. Soetomo. Hasil penelitian menunjukkan nilai rasio L/S setelah pemberian deksametason 4 mg/12 jam selama 2 hari pada ibu hamil dengan resiko persalinan preterm rata-rata 8,7 dengan rentang 3,5-20,8 dan setelah pemberian deksametason 6 mg setiap 12 jam selama 2 hari adalah 10,96 dengan rentang 4,4-23,1. Pemberian deksametason antara dosis 4 mg dan 6 mg setiap 12 jam selama 2 hari pada ibu hamil dengan resiko persalinan preterm tidak menunjukkan perbedaan nilai rasio L/S.**(FMI 2015;51:45-52)***

Kata kunci: *cortikosteroid, deksametason dosis 4 mg dan 6 mg, deksametason untuk pematangan paru, persalinan prematur, maturitas paru janin.*

ABSTRACT

*Betamethasone and dexamethasone are antenatal corticosteroids used in RDS (respiratory distress syndrome) reduction, the most frequent cause of infant prematurity. RDS is related to pulmonary strucure and function immaturity, which is measured with lecithin/sphyngomyelin (L/S) ratio as gold standard. No studies had been conducted comparing dexamethasone in different regiments. This study was conducted to analyze lower dexamethasone dose in enhancing fetal pulmonary maturity and to analyze dexamethasone use at a dose of 4 and 6 mg every 12 hours for 2 days for accelerating fetal lung maturation in women at risk of preterm birth on L/S ratio. This study, reviewed by the ethics committee of Dr. Soetomo Hospital, Surabaya, conducted from July 2013 to January 2014, used longitudinal prospective method involving two groups, dexamethasone 4 mg and 6 mg, administered intramuscularly twice daily for 2 days with total sample size 34 samples. Amniotic fluid samples were taken from women at risk of preterm birth with gestational age 28-34 weeks. Lecithin and shingomyelin levels in amniotic fluid were determined by ELISA method to calculate L/S ratio. The mean L/S ratio after dexamethasone dose of 4 mg twice daily for 2 days in women at risk of preterm birth were 8.7 with L/S ratio ranged 3.5 to 20.8 and after administration of 6 mg dexamethasone it was 10.96 with L/S ratio 4.4 to 23.1. In conclusion, L/S ratio between dose dexamethasone 4 and 6 mg was not different in women with preterm birth risk given every 12 hours for 2 days. **(FMI 2015;51:45-52)***

Keywords: *corticosteroids, dexamethasone at dose of 4 mg and 6 mg, dexamethasone for accelerating fetal lung maturity , preterm labour, fetal lung maturity.*

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INTRODUCTION

Prematurity is the leading cause of mortality and morbidity in infants. The most common cause of death in premature infants is respiratory distress syndrome (RDS) (Kamath et al 2011). RDS in premature infants associated with the structure and function of the immature lung. Immaturity of lung structure and function will lead to reduced production of surfactant by alveolar type II cells, so that will happen surfactant deficiency and leads to RDS (Mwansa-Kambafwile et al 2010). Surfactant is composed of 90% lipid and 10% protein, 76% of the lipid is in the form dipalmitoil phosphatidylcholine (DPPC), 13% phosphatidylgly-

cerol, phosphatidylinositol 4%, 3% phosphatidylethanolamine, sphingomyelin and phospholipids 2% other 2% (Lyra & Diniz 2007). Determination of the ratio of lecithin/sphingomyelin (L/S) is the gold standard of lung maturity test amniotic fluid, this is due to lecithin is the largest component of lung surfactant. The immature fetal lung examination if ratio L/S < 2.0, and is said to mature when the L/S ratio ≥ 2.0 (Haymond et al 2006).

Reduction strategies RDS in infants born prematurely is by administering antenatal steroids to women at risk of preterm birth before 32-34 weeks gestation (Wapner & Jobe 2011). Antenatal corticosteroids are widely used was betamethasone and dexamethasone. Dexamethasone and betamethasone are the only long acting glucocorticoids are structurally different isomers, namely the position of the methyl group at position 16 of ring structure that will result in different activity (Wapner & Jobe 2011, Vidaeff et al 2003). Both are able to cross the placenta in an active form with an efficiency comparable because it has a low affinity to maternal cortisol binding globulin (CBG) and slightly broken by enzymes that metabolize steroids in the placenta (Wapner & Jobe 2011, Brownfoot et al 2013). Betamethasone is available in two forms namely betamethasone sodium phosphate solution with t1/2 short 36-72 hours and betamethasone acetate suspension with a t1/2 is relatively long. Dexamethasone is generally in the form of dexamethasone sodium phosphate, a solution with a t1/2 36-72 h (Jobe & Soll 2004, Katzung 2004). Related controversy still going on antenatal corticosteroid dosing is optimal. Regimentation that is commonly used is 2 times the dose of 12 mg betamethasone intramuscularly at intervals of 24 hours and 4 times the dose of dexamethasone 6 mg at intervals of 12 hours intramuscularly. There has been no direct studies comparing dexamethasone with different doses regimentation. Betamethasone injection in Indonesia is hard to find, and more expensive, so use the stereoisomers betamethasone dexamethasone at a price that is now significantly cheaper and easier to obtain. Pharmacology suggests that administration of glucocorticoid corticosteroid with a lower total dose has the same effectiveness and lower side effects. So it is necessary to research on the effectiveness of dexamethasone with lower doses to accelerate fetal lung maturity with parameter L/S ratio.

MATERIALS AND METHODS

Subjects

This study is an observational study with cross-sectional approach over a period of seven months starting in July 2013-January 2014 The study population was pregnant women at risk for preterm labor in the delivery room IRD Hospital Dr. Soetomo. Selection of patients underwent consecutive sampling, in which all patients who meet the inclusion and exclusion criteria were taken as the study sample. Then the patients were divided into 2 groups, the treatment group dose dexamethasone 4 mg and dexamethasone treatment group were given a dose of 6 mg for 2 days every 12 hours (4x dose). Amniotic fluid taken at the time of delivery occurs between day 2 (48 hours) until the 7th day after the administration of dexamethasone. The sample size of each group were 17.

Inclusion criteria for this study were pregnant women with gestational age of 28 weeks up to 34 weeks less than that in confirmation with the complete history of antenatal ultrasound and or at risk of preterm birth and willing to sign informed consent. While the study exclusion criteria are pregnant women with the condition of diabetes mellitus, chronic hypertension, severe preeclampsia, fetal growth restriction, multiple pregnancy, the fetus suffered from major congenital abnormalities, diseases that cause the condition hiperandrogen (CAH), mothers who received steroid therapy for other indications, as well as pregnant women who are known or suspected contraindications or allergy to dexamethasone.

Data Analysis and Statistics

To evaluate the value of the ratio L/S between treatment groups dexamethasone 4 mg and 6 mg dexamethasone treatment group in pregnant women with gestational age of 28 weeks to less than 34 weeks are at risk of preterm labor is used statistically independent t-test if normal distribution and test Mann-Whitney if the distribution is not normal, whereas to determine the relationship between the value of the ratio L/S of the gestational age and BMI (Body Mass Index) is used Pearson correlation test if a normal distribution and Spearman correlation test if the distribution is not normal.

RESULTS

Number of samples who fulfill inclusion criteria from July 2013 until January 2014 were 34 patients, divided into 17 patients for control group and 17 patients for treatment group. Sample of study characteristics are shown in Table 1.

Standard curve made using standard respectively 6 standard lecithin and sphingomyelin standards. Standard lecithin were made in the concentration range between 0 to 120 ng/ml whereas sphingomyelin standard were

made in the concentration range between 0 to 16 ng/ml which will be read at a wavelength of 450 nm with an ELISA Reader/Microplate Reader (Table 2). From the absorbance values will be known value of lecithin and sphingomyelin levels. Gestational age is an important variable that can affect fetal lung maturity. Table 3 shows the distribution of samples based on changes in the value of L/S ratio against gestational age in the group of dexamethasone 4 mg and 6 mg dexamethasone group.

To determine differences in the L/S ratio between groups 28- gestation < 30 weeks, 30 to < 32 weeks, 32 - < 34 weeks in the treatment group dexamethasone 4 mg or 6 mg of dexamethasone treatment group conducted One Way ANOVA Test. Based on the obtained results of the ANOVA test of significance of P 0.000 (p < 0.05) which means that there are differences in the ratio of lecithin/sphingomyelin significantly in group 28- gestational age < 30 weeks, 30 to < 32 weeks, 32 - < 34 weeks for both treatment groups dexamethasone 4 mg and 6 mg dexamethasone treatment group (Table 3). To determine the relationship between gestational age with the value of the ratio L/S Pearson correlation test. Obtained statistically significant value of 0.000 in the dexamethasone group dexamethasone 4 mg and 6 mg groups showed that the correlation between gestational age with L/S ratio was statistically significant higher gestational age where the value of the ratio L/S is also higher.

Table 1. Sample of study characteristics

Sample Characteristics/Patient	Number % 4 mg	Number % 6 mg	Mean ± SD 4 mg	Mean ± SD 6 mg
Maternal age				
16 – 25 th	9	7	25.6	26.9
26 – 35 th	7	8	± 6.6	± 6.7
36 – 45 th	1	2		
BMI				
< 18.5	0	1	23.9	22.5
18.5 – 24.9	10	11	± 2.6	± 3.3
25.0 – 29.9	7	5		
30.0 – 34.9	0	0		
Graviditas				
Primigravida	11	8		
Multigravida	6	9		
Risk of Preterm Birth				
KPP	10	9		
PPI	4	4		
PP	0	3		
Heart disease	2	1		
Others	1	1		
Gestational Age				
28 – < 30 week	5	3		
30 – < 32 week	7	8		
32 – 34 week	5	7		
Mode of Delivery				
Perabdominam	7	8		
Pervaginam	10	9		
Birth Weight (gram)				
1000 – 2000	16	15		
2000 – 3000	1	2		
AS 1 minute				
< 3	1	4		
3 – 6	4	3		
> 6	12	10		
AS 5 minute				
< 3	1	1		
3 – 6	1	2		
> 6	15	14		

Table 2. Levels and absorbance standard lecithin and sphingomyelin standards amniotic fluid samples at 450 nm wavelength

Lecithin standard	Level ng/ml	Absorbance	Sphyngomyelin Std	Level ng/ml	Absorbance
Std 1	0	0.154	Std 1	0	0.188
Std 2	7.5	0.214	Std 2	1	0.226
Std 3	15	0.278	Std 3	2	0.259
Std 4	30	0.399	Std 4	4	0.342
Std 5	60	0.646	Std 5	8	0.517
Std 6	120	1.173	Std 6	16	0.874
Line Equation	y = 0.008 x + 0.148		Line Equation	y = 0.043 x + 0.178	

Body Mass Index (BMI) is one of the clinical characteristics that represent the nutritional status of pregnant women. To determine the relationship between BMI with the value of the ratio L/S Pearson correlation test. Based on the results of the Pearson correlation test p value = 0.000 both in the dexamethasone group 4 mg and 6 mg means that there is a significant correlation between BMI with the ratio L/S which showed higher BMI, the value L/S ratio is also higher (Figure 1).

To determine differences in the effect of dexamethasone on the ratio of lecithin/sphingomyelin on dexamethasone 4 mg dose group compared to dexamethasone 6 mg dose group used independent sample t test. Based on a statistical test for unpaired 2 groups on the value of the ratio L/S obtained 0.102 significant value because the value of p > 0.05 means that there is no difference in the ratio L/S in the therapeutic dose dexamethasone compared to dexamethasone 4 mg therapeutic dose of 6 mg. However, the average ratio L/S at 6 mg dexamethasone group showed a tendency to increase on average by ± 25% compared to the dexamethasone 4 mg group, but this difference was not statistically significant due to a coefficient of variation in this study is quite large.

DISCUSSION

Respiratory distress syndrome (RDS) is a condition in which the pulmonary alveoli do not develop, causing difficulty in breathing process. Some literature indicates that RDS is derived from the inability of surface active phospholipid production in fetal lung (Cunningham et al 2010).

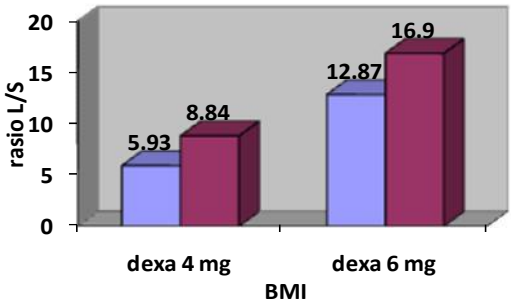

Figure 1. Changes in value ratio L/S against BMI in treatment group dexamethasone 4 mg and 6 mg

Table 3. Changes in value ratio lecithin/sphingomyelin against pregnancy in groups dexamethasone 4 mg and 6 mg

Dexamethasone 4 mg				Dexamethasone 6 mg				Significance Group Dexamethasone 4 mg and 6 mg (p)
Patient's Initial	Gestational Age (weeks)	Ratio L/S	Mean ± SD	Patient's Initial	Gestational Age (weeks)	Ratio L/S	Mean ± SD	
RO		3.5		SH		4.4		
CN		4.0		EY		6.5		
NW	28 – 30	3.6	4.8 ± 2.0	SW	28 – 30	7.7	6.96 ± 1.6	0.513
TM		4.6		DL		7.8		
LS		8.3		SR		8.4		
IN		7.5		MP		8.1		
TT		7.6		SE		8.2		
GT		9.4		LS		9.4		
AM	30 – 32	4.1	7.7 ± 1.9	SA	30 – 32	9.5	9.4 ± 1.3	0.805
DS		7.4		DN		9.8		
DI		7.6		SP		11.6		
WN		10.2						
NH		9.0		LD		13.2		
NN		11.2		SS		13.3		
YY	32 – 34	14.1	14.3 ± 4.6	SM	32 – 34	19.9	15.8 ± 4.8	0.752
AT		16.5		RB		10.3		
RW		20.8		ST		23.1		
				SN		15.2		
Significance Pregnancy Group against the ration L/S		p = 0.000		Significance Pregnancy Group against the ration L/S		p = 0.000		

Lecithin and sphingomyelin concentration increases rapidly at the end of pregnancy, so checking the ratio L/S is an accurate test to determine fetal lung maturity, and established as the gold standard examination of fetal lung maturation, although there is no easy and fast method to determine the lecithin in the amniotic fluid, so it is necessary to develop a method to determine the ratio L/S with a faster time, cheap, objective, high sensitivity and specificity to assess fetal lung maturity. In this study developed a method of determining the ratio L/S by using enzyme-linked immunosorbent assay (ELISA) (Anaokar et al 1978).

Characteristics of maternal age in the study by an average of 25.6 on dexamethasone 4 mg group and an average of 26.9 on average 6 mg dexamethasone group, with coefficients of variation were small so variable maternal age did not affect the results of the study because are in the same range. According to research by the WHO, women who are pregnant at the age less than 20 years, is likely to experience preterm. Because immature mother's condition, both in the knowledge, psychological, and organs. Mothers who delivered preterm at the age below 20 years and above 35 years also had a tendency to produce offspring with different fetal outcomes compared with term delivery.

Maternal BMI (Body Mass Index) suspected to play an important role in the etiology of preterm. BMI's mother is concerned about the condition of obesity in

pregnancy. Condition of pregnant women who are obese will affect placental development and embryo development in the early stages so will result in the development of the fetus. Pregnant women who are obese can lead to some good effect on the mother or the baby is born. Some research suggests that a BMI of 30 kg/m 2 or more is a risk factor for gestational diabetes occurs, preeclampsia, preterm labor, fetal macrosomia and infant mortality in the uterus. In this study contained the highest BMI range 18.5 - 24.9 BMI group by 65% in the treatment group dexamethasone 4 mg and 6 mg treatment groups.

BMI variable analysis showed no difference in mean BMI in both treatment groups, in which the 4 mg dexamethasone treatment group mean BMI 23.9 and at 6 mg dexamethasone treatment group average of 22.5. Statistically with an unpaired t test was also not significantly different between BMI groups dexamethasone 4 mg and 6 mg dexamethasone group so variable BMI is not affected the results with $p = 0.178$ ($p > 0.05$)

Research by Norwood (2013) showed that pregnant women who are obese will reduce 11 - β HSD 2 enzyme is an enzyme that inactivates cortisol (active glucocorticoid) into cortisone (inactive glucocorticoids). Another study by Bose et al (2009) showed that pregnant women who are obese happen β over-expression of the enzyme 11 - HSD 1 due to stimulation of the HPA axis. The enzyme 11 - β HSD-1 is an enzyme that converts cortisone into cortisol. Maternal cortisol will cause a feedback mechanism to the release of p-CRH results in increased secretion of adrenal cortisol mother and the fetus, so that there will be an increase in cortisol in pregnant women. Cortisol will increase the incorporation of choline, acetate, palmitate, and glycerol into total phosphatidylcholine and disaturated phosphatidylcholine and phosphatidylglycerol stimulates formation. Increased cortisol will increase the ratio L/S (Jobe & Ikegami 2001). So at that obese pregnant women will experience early lung maturation. This is consistent with the results of the study there was a trend increase in the ratio L/S of the BMI in the intervention group dexamethasone 4 mg and 6 mg, which at 6 mg dexamethasone treatment group value of the ratio L/S on average higher than 4 mg treatment groups.

Parity is the number of births the mother has done. In this study occurred in the largest gravidity first pregnancy (primigravida) to 4 mg dexamethasone treatment group was 65% and 53% in pregnancy multigravida for a dose of 6 mg treatment groups. 2-3 Parity is the most secure parity terms of the maternal deaths (Prawirohardjo 2005). Parity 1 and parity of more than 3 had higher mortality rates. Mothers with low parity tends to a baby who is not mature or are there complications because it is a first experience on the reproductive ability of the mother and the disease is likely to arise in pregnancy and childbirth. While mothers with high parity (giving birth more than 3 times) tend to experience complications that ultimately affect the delivery (Sulistyawati 2011). In this study the amount of labor is restricted to subjects who gave birth to no more than 3 times that gravidity variable does not affect the study results.

In this study the biggest risk factor for preterm labor is premature rupture of membranes (KPP) is 59% in the dexamethasone 4 mg and 6 mg dexamethasone treatment group was 53%. This is due to premature rupture of membranes occurred direct relationship between the outside world and the room in the uterus, thus facilitating the occurrence of intrauterine infection there will be a condition of asphyxia and hypoxia although infants born at term. If the rupture at the age of 34 to 36 weeks of pregnancy there is an increased risk of infant morbidity and mortality due to RDS.

Infant outcomes that can be observed is the birth weight and Apgar score. Babies are born with a body weight > 1750 grams is likely to experience very little good RDS antenatal steroid therapy or not (Amanullah et al 2002). In the study of the distribution of the largest sample in the 1000 - 2000 g birth weight. This is consistent with the development of the baby's weight based on gestational age at which the age of 28 - 34 weeks gestational weight babies were in the range 1000 to 2100 grams (Cunningham et al 2010).

Apgar Score can provide additional information of clinical outcomes baby's lungs. Value fifth minute Apgar score is a component which is very useful in predicting multisystem organ dysfunction, acute (Green et al 2007). In this study the distribution of the sample based on the value-minute Apgar score is the most pertamamaupun fifth minute Apgar score score > 6 This suggests that the dose dexamethasone 4 mg or 6 mg of providing clinical outcomes baby's lungs are good, so the possibility of risk of RDS will also be small.

Still the value of Apgar score < 3 and 3 - 6 in each treatment group even though the value of the ratio L/S > 2 due to the Apgar score assessment is done after the baby is born so it can not be used to predict the baby has RDS, in addition to the value of Apgar score is determined only by respiratory parameters (respiratory), but also influenced by a variety of clinical conditions of infants and other laboratory tests such as skin color (Appearance), pulse (Pulse), reaction to stimuli (Grimace) and muscle tone (Activity), and is determined after the baby is born without any risk of intrauterine hypoxia and, thus determining the risk of having a baby

before birth, RDS is the determination of the amount of surfactant baby value L/S ratio. In this study does not make observations to the clinical condition of preterm birth due to limitations of time and cost of research.

Mode of delivery in study subjects to determine how sampling amniotic fluid. The standard way of sampling the amniotic fluid recommended for fetal lung maturity test is amniocentesis, but according to research by Visnjevac 2010 stated that there was no significant difference between the way the decision through the vaginal pool amniotic fluid when vaginal delivery or perabdominam. Based on the mode of delivery, in the study conducted in the biggest way vaginal delivery is 59% in the 4 mg group and 53% in the largest group of 6 mg perabdominam while the mode of delivery as much as 41% for dexamethasone 4 mg group and 47% for groups of 6 mg dexamethasone.

Gestational age is an important variable that can affect fetal lung maturity. In this research group gestational age 28 - 34 weeks with the goal of population are at the same stage in the development of the lungs. Based on the research results Amanullah et al (2002) RDS incidence is more common in gestational age below 34 weeks because at this gestation fetal lungs are in the saccular stage of lung development. Premature labor happens during the saccular stage of lung development kanalikular and very often causes RDS due to poor development and poor peripheral airway cells of lung maturation is important in the maturation of the lung such as cell type 2 pneumocytes and inadequate antioxidant response to a sudden increase in oxygen. The development of the alveolar-capillary interface is bad for saccular phase can lead to alveolar-capillary dysplasia and other disorders including RDS after the fetus is born preterm (Kotecha 2000).

To determine whether there are differences in average gestational age between treatment groups dexamethasone 4 mg and 6 mg dexamethasone groups used the Mann Whitney test and p value > 0.05 at each gestational age group, which means there is no difference in the average gestational age significant between groups, so that the variable gestational age in both groups were in the same range.

From some references say that the older gestational age will be less risk of RDS, this is because the amount of surfactant that is higher, because the surfactant is lecithin largest composition, the lecithin concentration also increased according to the increase in gestational age. This is consistent with the results of this study that there is a significant correlation between the ratio L/S with a mean gestational age of the pregnancy the older the higher the ratio L/S with a p-value of 0.000 using Person correlation test.

Lecithin is the largest component of surfactant which serves to lower the surface tension at the air liquid interface layer dialveolar so will prevent alveolar collapse when the end of the expiratory phase of respiration. In addition, the surfactant also contains four kinds surfaktant associated protein (SP) that SP - A, SP - B, SP - C and SP - D, surfactant protein A, which has the most important role of SP - A. SP - A and SP - D are hydrophilic which serves as the body's natural defenses. SP - B and SP - C are hydrophobic proteins and is required for the creation of surface tension reduction in the optimum manner to promote rapid adsorption of surfactant phospholipids along the alveolar surface (Harding & Hooper 2009).

Dexamethasone is due to the synthesis of fluorinated glucocorticoids that can penetrate the placental blood barrier, where most of dexamethasone would be metabolized by the placental enzyme (enzyme 11 β-HSD) become inactive form with a protein binding of 64%. In human plasma deksmetason primarily bind to albumin which has a large capacity but low affinity, and a little bind to cortisol binding globulin (CBG).

Dexamethasone has a 25 times higher affinity than cortisol to the glucocorticoid receptor, but the potential is lower than the genomic dexamethasone betamethasone due to differences in the structure of the configuration of the methyl group dexamethasone and betamethasone. Dexamethasone has a long half-life with lower peak levels, so as not to exceed the levels of toxicity in the blood (Erhuma 2012, Manojlović-Stojanoski et al 2012).

To determine the effect of infant lung function maturation of dexamethasone in women with preterm birth risk to the L/S ratio as a parameter of fetal lung maturity, in this study used a dose of 4 mg and 6 mg given every 12 hours for 2 days intramuscularly. Selected dose of 4 mg is lower because the pharmacological effects of corticosteroids given where the higher dose will not increase benefits but will increase the risk of side effects.

Dexamethasone intramuscularly chosen because the intramuscular route has zero order kinetics, so that the slower release and longer duration. Intravenous administration is not recommended because it will give you exposure to steroids in pregnant women and infants with high concentrations in the early stages so it will increase the risk of side effects due to dexamethasone would rapidly penetrate the placenta. In this study, dexamethasone given 4 times the dose for 2 days

because of antenatal corticosteroid therapy is done resembles endogenous corticosteroid exposure that occurs during pregnancy in which the induction of endogenous cortisol in the mother also occur for 48 hours (2 days), so that the duration of dexamethasone was also given for 2 days. In addition, based on preliminary research that states that babies born less than 2 days of exposure to corticosteroids is still in need of resuscitation and ventilator compared to babies born between day 2 to day 7 after exposure to corticosteroids (Sekhavat et al 2011, Wapner & Jobe 2011).

Prior to the examination of the ratio L/S sample test, conducted by making a standard curve of phosphatidylcholine and sphingomyelin standard curve. Based on the results of the ELISA Reader absorbance readings at a wavelength of 450 nm of standard phosphatidylcholine and sphingomyelin obtained standard line equation y = 0.008 x + 0.148 for standard phosphatidylcholine and y = 0.043 x + 0.178 for the standard slope sphingomyelin with R2 = 0.99. From the line equation is used to calculate the levels of phosphatidylcholine and sphingomyelin levels of amniotic fluid test sample. In this research, a standard dilution because the enzyme is unstable if it is in a low concentration, so the standard is made with a dense concentration.

At 4 mg dexamethasone treatment group obtained an average value of L/S ratio of 8.7 with a range of values L/S ratio from 3.5 to 20.8 and the standard deviation (SD) of 4.77 for the treatment group dose dexamethasone 4 mg . While at 6 mg dexamethasone treatment group obtained an average value of L/S ratio of 10.96 with a range of values from 4.4 to 23.1 and the SD value of 4.79.

Based on the obtained unpaired T test significance value 0.102 ($p > 0.05$) means that there is no significant difference between the L/S ratio in the therapeutic dose dexamethasone compared to dexamethasone 4 mg therapeutic dose of 6 mg. However, the average ratio L/S at 6 mg dexamethasone treatment group showed a tendency to an increase of ± 25% compared to 4 mg dexamethasone treatment group, but this difference was not statistically significant between the therapeutic dose dexamethasone 4 mg to 6 mg dose dexamethasone therapy.

There has been no studies directly comparing different doses of dexamethasone for fetal lung maturation function. Antenatal dexamethasone with standard dosing regimen (dose of 6 mg 4 times the dose interval of 12 h) showed that the minimum concentration in the fetal circulation has been exceeded, so the administration of dexamethasone at a dose lower than the usual dose is given may have been able to reach the peak response, so that exposure mother and fetus to corticosteroids can be reduced by 25% of the usual dosage regimen is a dose of 4 mg 4 times the dose interval of 12 hours (Ballard & Ballard 1995).

This study has provided data on the proportion of fetal lung maturity after administration of antenatal dexamethasone therapy at a dose of 6 mg (usual dose is often used) and a dose of 4 mg that we submitted. By knowing the amount of proportion and the difference between the dose of antenatal dexamethasone 6 mg and 4 mg is at least expected to provide evidence that the administration of lower doses can also give effect to the increase of the ratio L/S as a parameter of fetal lung maturation. Because in this study there was no significant difference in the dose dexamethasone 4 mg/12 hours and dexamethasone dose of 6 mg/12 hours for 48 hours against the L/S ratio in pregnant women at risk of preterm labor, so it is recommended in cases of preterm labor to accelerate the maturity used fetal lung dose dexamethasone 4 mg every 12 hours for 2 days and further studies will be needed dose of 4 mg dexamethasone effects on fetal lung maturation other parameters (such as fosfatidilglierol) as well as a dose of 4 mg dexamethasone effects on clinical condition of infants (RDS, IVH, and NEC).

CONCLUSIONS

Dexamethasone doses of 4 mg and 6 mg every 12 hours for 2 days in pregnant women at risk of preterm labor results in similar effect in the value of ratio L/S ratio.

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