

# PREDICTORS OF FEEDING ACHIEVEMENT IN NEONATES BORN FROM PREECLAMPSIA MOTHERS

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**Abstract** – The aim of this study is to observe maternal and neonates predictive factors for successful feeding. Feeding intolerances were associated with many factors, such as premature baby, sepsis, and necrotizing enterocolitis. Feeding achievement is important to achieve adequate nutrition. Other factors that influence successful feeding will be assessed in this study. This is a cross sectional study using secondary data obtained from medical records of 72 subjects from mothers and neonates, recruited with consecutive sampling. This study performed in Cipto Mangunkusumo Hospital, mother who developed preeclampsia, or complication from preeclampsia with neonates 28-37 weeks gestational age. Univariate, bivariate, and multivariate analyses were performed in this study. The results showed that a large proportion of the babies were born from mothers aged 31-35 years old, giving birth through sectio caesaria delivery, and having severe preeclampsia, and non hypoxic SDAU. Most of the babies born at gestational age  $\geq 32$  weeks and females. The most of the babies born with a birth weight of 1,000-1,500 grams and 1,501-2,000 grams weeks were not different, the most babies not IUGR, being assisted with CPAP, having an APGAR score  $\geq 7$  at 5th minute. Multivariate analyses revealed the gestational age and clinical symptoms were predictor factors for successful feeding in neonates. Neonates successful feeding in median 9.5 days range from 3.5 to 15.5 days. The conclusion in this study were the predictor factors for successful feeding in neonates were gestational age more than 32 weeks and the absence of clinical symptoms.

## INTRODUCTION

Preeclampsia is a potentially fatal disorder affecting mother and fetus during pregnancy. Preeclampsia occurs in 2-7% of healthy nulliparous (Cnossen *et al.*, 2008). According a study conducted in the United States, the incidence of preeclampsia is 23.6 of 1,000 births another study has identified that 5-10% women with hypertension in pregnancy experienced preeclampsia (Wagner *et al.*, 2004; Cunningham *et al.*, 2010; Wiknjosastro, 1992).

It is essential to understand the pathogenesis of preeclampsia and develop a strategy to manage the impact of maternal preeclampsia in neonate. The placenta in mother who develop preeclampsia is not adequately implanted. This may cause spiral arteries to fail in developing uteroplacental blood vessel in early pregnancy. As a result, blood flow from maternal circulation to the placenta is restricted and this condition causes fetal hypoxia

(Wiknjosastro, 1992). In addition, nitric oxide pathway is impaired and nitric oxide level decreases (Rugolo *et al.*, 2011). Consequently, the fetus is at risk of preterm birth, acidosis, intra-uterine growth retardation, neonatal asphyxia, and still birth (Doddamani and Doddamani, 2014). Fetal hypoxia leads to short-term consequences including respiratory distress syndrome, thrombocytopenia, neutropenia, septicemia, bronchopulmonary dysplasia, necrotizing enterocolitis, feeding intolerance, intraventricular hemorrhage, cystic periventricular leukomalacia, and still birth. Meanwhile, long-term impacts include growth faltering and difficulty to catch up and overweight or obesity during the adolescent period (Rugolo *et al.*, 2011).

There are challenges in caring neonates who born prematurely or with intrauterine growth retardation from preeclampsia mother. Gastrointestinal immaturity, oromotor disorders, and impaired

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intestinal motility are common in preterm neonates (Harahap *et al.*, 2013; Wahyuni, 2011; Neu, 2007). These conditions have caused delay in enteral feeding and prolonged the use of parenteral nutrition. Long-term parenteral nutrition impairs hormonal and lactase activities, nutrient absorptions, gastrointestinal structure and functions, gut mucosal growth, which potentially cause gut mucosal atrophy (Mishra *et al.*, 2011). These conditions will lead to feeding intolerance especially in preterm and IUGR babies will cause feeding intolerance, which should be monitored in preterm babies and those who born with intrauterine growth retardation.

Feeding achievement is reached when babies are fully fed with amount of 120 mL/kg body weight per day. Feeding intolerance is a condition in which there is evidence of increased gastric residual (Andersen, 2012) abdominal distention, discoloration of abdominal wall, bloody feses, and vomiting (Andersen, 2012; Yue-Feng *et al.*, 2014; Rundjan *et al.*, 2013). Clinical signs, including increased abdominal circumference, abdominal distention, and bowel dilatation from the x-ray examination can be used as indicators for feeding intolerance (Rundjan *et al.*, 2013). In another study, Doppler ultrasound examination is determine the blood flow in mesenteric artery which can be used to assess feeding intolerance to determine the blood flow in mesenteric artery necrotizing in order to indicate feeding intolerance. Thus, necrotizing enterocolitis can be prevented (Khodair *et al.*, 2014). In Cipto Mangunkusumo Hospital, feeding intolerance is commonly found in babies born from preeclampsia mother. However, there are limited study to determine the causes of feeding intolerance in those babies. Therefore, this research is aimed to determine predictors of feeding intolerance in babies born from can be prevented.

## METHODS

### Study setting

This study is performed in Cipto Mangunkusumo Hospital as a national referral centre in Jakarta. Subject of this study were babies born with 28-37 weeks gestational age from both uncomplicated and complicated preeclampsia mother.

### Study design

This is a cross-sectional study that carried out from mei until July 2015. The sample size from formula

descriptive design and multivariate analysis were 72 subjects. We collected from medical record mothers and neonates. The data of maternal and infant characteristics are summarized descriptively. The mothers are classified into preeclampsia and complicated preeclampsia according to ACOG criteria preeclampsia or complication preeclampsia, according criteria from The American College of Obstetrician and Gynecologists. The mothers are classified into preeclampsia and complicated preeclampsia according to ACOG criteria. Only subjects of whom medical records were complete were included in this study. We analysis univariate, bivariate, and multivariate. As multivariate analysis, a logistic regression was conducted to determine predictors of feeding achievement of babies born from mothers with preeclampsia. Only variables that have p-value less than 0.25 will be included in the multivariate analysis (Dalhan, 2013).

### Sampling method

This study use consecutive sampling. To determine prediction of feeding achievement of babies, univariate, bivariate, and multivariate were analysed.

### Data collection process

This study has ethical approval from ethics commission for medical research at the Medical Faculty of Indonesia University with number 2400/UN2.F1/Etik/2015. Data were collected from babies and mother's medical record ethical approval, we collecting data from babies who born from the preeclampsia mother and medical record from mothers. Exclusion criteria with 28-37 weeks gestational age, complete medical record both from mothers and babies, and babies who born from preeclampsia mother and complication preeclampsia. Exclusion criteria : babies with mayor congenital anomalies, proven sepsis from birth, babies with duct dependent heart disease, and babies get manual positive pressure ventilation.

### Dependent variable

The dependent variable was feeding achievement from babies who born from the preeclampsia mother.

### Independent variable

The independent variable divided from babies and mothers. From babies we found the characteristic:

gender, gestational age, birth weight, ventilation support, APGAR Score, admitted the babies, patent ductus arteriosus (PDA) or hyaline membrane disease. The characteristic mothers : age from mother, the most common birth methods, systolic and diastolic ratio at umbilical artery (UA) velocity perform in the mothers.

Since babies received minimal enteral feeding below 25 mL/BW until started. Full feed tolerance is achieved within 14 day (2 weeks). The types of enteral feeding were breast milk, donor breast milk, formula milk, breast milk and donor, or combined breast milk and formula milk.

Clinical intolerance signs such as increased gastric residual, abdominal distention, discoloration of abdominal wall, bloody feces, vomiting, and bleeding from orogastric tube (OGT). Radiological examination may showed intestinal thickening or pneumatosis intestinal which support the diagnosis of NEC.

### Data analysis

The data including subjects' characteristics, laboratory and imaging results, preeclampsia complications, the time of minimal enteral feeding was started, and the achievement full feeding were collected from medical records and recorded in study data collection forms. Data were analysed using SPSS 21 for Windows. The data were summarized in narration and tables.

## RESULTS

### Subjects' characteristics

The number of the participants completed the study was 72 babies, of whom mostly are females 41 (56.9%) subjects. Fifty four point two percent of the babies were born with a gestational age of  $\leq 32$  weeks Around 37.% babies were born with a birth weight of 1000-1500 g and 1501-2000 g. The majority of subjects did not experience intrauterine growth retardation 72.2% subjects. CPAP was used as ventilation support in 45 cases (62.5%) around 77.8% babies were born with APGAR score at 5 minute  $\geq 7$ .

The age of subject's mother were 31-35 years. Systolic and diastolic ratio at umbilical artery (UA) velocity perform in the mothers caused not hypoxia in 43 (59.7%) subjects.

### Infant feeding achievement

MEF is expected to start at least at the fifth day of life and full feed tolerance is achieved within 14 day

(2 weeks). The MEF  $\leq 5$  days mostly in 47 (65.3%) subjects. And full feed within 14 days in 27 (37.5%) subjects. The types of enteral feeding mostly breast milk and formula milk in 43 (59.7%) subjects.

In this study, the majority of the subjects did not have clinical intolerance signs in 37 (51.4%) subjects and radiological imaging was not performed to almost half of the study population in 33 (45.8%), in whom feeding started early and clinical intolerance signs were not found. The most frequently found intolerance sign was bleeding from orogastric tube (OGT) in 16 (22.2%) subjects. NEC was found in 20,8% of the subjects by radiological finding.

### Bivariate analysis

Kolmogorof-Smirnov test was used for abnormal distributed data and Chi square test for normal distributed data. For normally distributed data, a chi square test was used. P-value was set as  $p < 0.05$ . Odds ratio and p-value were used to determine the association between maternal variables and full feed achievement.

There are association between subject, maternal characteristics, and full feed achievement. In this study, gestational age  $p < 0.001$  (OR 9.65), birth weight  $p < 0.001$  (OR 9.743), clinical intolerance  $p < 0.001$  (OR 14.154), radiologic finding  $p < 0.001$  (OR 10.000), and infection  $p < 0.001$  (OR 7.341), were significantly associated with full feeding achievement  $p < 0.05$ . The result can be seen in Table 1.

### Multivariate analysis

Multivariate analysis was conducted by including variables associated with full feeding achievement with  $p < 0.25$  into the analysis. The results can be seen in Table 2.

Variable included in the multivariate analysis were gestational age, birth weight, clinical intolerance, radiologic finding, and infection. Was used to analyze categorical dichotomous data. From the data shown in the Table 2, it can be concluded that babies are highly likely to achieve full feeding if the gestational age  $> 32$  weeks and clinical intolerance was absent.

## DISCUSSION

Thirty nine subjects were born at less than 32 weeks and 56,9% of the subjects were female. IUGR were found in 27,8% of the subjects. The highest number of female infants jenis in 41 (56.9%) subjects, birth

**Table 1.** The association between infant and maternal variables and full feed

Variables	Full feed				p	OR	95% CI		
	Yes	%	No	%			Min	Max	
Gestational age	> 32 weeks	21	29.2	12	16.7	<0.001 <sup>b</sup>	<b>9.625</b>	3.133	29.569
	≤ 32 weeks	6	8.3	33	45.8				
Gender	Male	15	20.8	16	22.2	0.097 <sup>b</sup>	2.266	0.855	6.001
	Female	12	16.7	29	40.3				
IUGR	No	23	31.9	29	4.3	0.064 <sup>a</sup>	3.172	0.932	10.796
	Yes	4	5.6	16	22.2				
Birth weight	> 1500 grams	22	30.6	14	19.4	<0.001 <sup>b</sup>	<b>9.743</b>	3.060	31.020
	≤ 1500 grams	5	6.9	31	43.1				
APGAR score at the 5 <sup>th</sup> minute	≥ 7	24	33.3	32	44.4	0.141 <sup>a</sup>	3.250	0.832	12.693
	< 7	3	4.2	15	20.8				
Type of feeding	Breast milk	2	2.8	8	11.1	0.302 <sup>a</sup>	0.370	0.072	1.889
	Mixed	25	34.7	37	51.4				
Clinical intolerance	No	23	31.9	13	18.1	<0.001 <sup>a</sup>	<b>14.154</b>	4.087	49.015
	Yes	4	5.6	32	44.4				
Radiologic finding	Yes	24	33.3	20	27.8	<0.001 <sup>a</sup>	<b>10.000</b>	2.628	38.058
	No	3	4.2	25	34.7				
Infection	No	19	26.4	11	15.3	<0.001 <sup>b</sup>	<b>7.341</b>	2.518	21.398
	Yes	8	11.1	34	47.2				
Preeclampsia	Severe preeclampsia	9	12.5	22	30.6	0.197 <sup>b</sup>	0.523	0.194	1.408
	Complicated	18	25	23	31.9				
SDAU	No hypoxia	17	23.6	26	36.1	0.664 <sup>b</sup>	1.242	0.466	3.309
	Hypoxia	10	13.9	19	26.4				

a= Fisher's chi square

b= Pearson chi square

**Table 2.** Multivariate analysis of factors associated with full feeding achievement.

Variable	CCoefficient	p	OR (95% CI)
GA ≤ 32 weeks	2.193	<b>0.002</b>	8.959 (2.272-35.328)
Infection	1.365	0.069	3.916 (0.899-17.052)
Intolerance	1.699	<b>0.027</b>	5.470 (1.212-24.689)
Constanta	-1.883	0.002	0.152

weight is as much as between 1,000-1,500 g and 1,501-2,000 g in 27 (37.5%) subjects. IUGR babies in 20 (27.8%) subjects. The other studies found 71% babies weighing more than 2500 g at birth were born from severe preeclampsia mother Twenty percent of the babies were IUGR (Gawde and Bhosale, 2014). WHO found that IUGR 75% in Asia especially in Southeast Asia (De Onis *et al.*, 1998). Helping and persuading mothers to get adequate nutrition is

essential. However, nutrition is not the main cause of fetal hypoxia in preeclampsia mother.

Most babies born with assisted ventilation with CPAP are 62.5%. In this study of the preeclampsia mother was referral to Cipto Mangunkusumo Hospital with fetal distress 20%. come to RSCM with fetal distress. Around 29.2% of the mother who got seizure and pulmonary edema, delivered the baby with C-section using general anesthesia. Due

to this condition, low APGAR score in the subjects could be caused by either hypoxia condition or anesthesia effect.

Vats K and Paul M found that APGAR score in 5 minutes > 7 in 74 (75.5%) subjects and < 7 in 24 (24.5%) (Vats and Paul, 2016). In this study mostly APGAR Score at 5th minute  $\geq$  7 in 56 (77.8%) subjects. APGAR Score in 5 minutes is important to predict the hypoxia condition in neonates and parameter the success of resuscitation.

Before 2014, change to: breastfeeding in CMH was very challenging due to mother's condition, such as mothers were to sick, the mother passed away, or the mothers were too busy. In the late 2014, the mothers were motivated and persuaded to express breast milk. Sick babies were given breastmilk to prevent infection and NEC. A RCT study showed that fresh breastmilk is preferred than donor human milk/formula milk. The incidence if NEC in babies receiving breastmilk was only 3% (Dutta *et al.*, 2015) Feeding less than 4 days reduce the incidence of NEC compared to feeding give between 5-7 days, with relatif risk ratio 0.89 (Barone *et al.*, 2013).

Around 42 subjects was infected in this study. The infection was predicted came from mother infections or after delivery. Prevention infection were done in various ways to decrease the growth of bacteria, such as intervention with faster feeding. Prevention with 6 steps : intervention with faster feeding with breast milk, infection control measures, physical intervention, intervention with immunomodulators, immunization, prophylactic antibiotics, and antibiotics for mothers with ruptured membranes (Isaac, 2014).

The majority age of subject's mother was 31-35 years in 23 (31.9%) subjects, it's different with study in Yogyakarta that majority age of the subject's mother was 21-25 years old and 20-30 years old. (Djannah and Arianti, 2010). Preeclampsia is higher in women childbearing age in this study, differ from the theory of preeclampsia, which the incidence higher in teenager, this study found that incidence of preeclampsia was higher in women in childbearing age.

C-Section is known as the most common birth method in 68 (94.4% subjects). Similar with study in Italian they found C-section in 86.2% preeclampsia mothers (Corvaglia *et al.*, 2014). Different with study in India in 2009. Tho common birth method was spontaneously in 42.6%. From 61 baby birth methods spontaneously, 26 died in perinatal period (Dhananjay

*et al.*, 2009).

Study in Italiy show that 86,2% of preeclampsia mothers gave birth by C-Section method (Corvaglia *et al.*, 2014). On the other hands, spontaneus birth method is often used in developing country such as India: with 42,6% birth. Dhananjay refers that 26 out of 61 babies passed away in perinatal period due to thes method (Dhananjay *et al.*, 2009).

The mother preeclampsia mostly have UA can't became hypoxia in fetus in 43 (59.7%) subjects. Nine subjects found absent end-diastolik flow (12.5%) and 1 (1.4%) subject reverse end-diastolic flow. From nine subjects with absent end-diastolik flow, only 3 subjects delivery IUGR. In this study, the mother was quickly treated so the fetus distress experience long term hypoxic condition (Torres *et al.*, 1995). The other study stared that absent end diastolic flow may caused IUGR to the baby. In this study found that the mother is quickly treated so the fetus does not take hypoxia for too long.

Mostly babies from preeclampsia mothers easy feeding in 37 (51.4%) subjects, there are no complaints about breast milk and radiological examinations were not performed on 33 (45.8%) subjects because the baby could feed quickly. NEC performed in 15 (20.8%) subjects and bowel wall thickening from radiological examination in 13 (18.1%) subjects, in clinical manifestation we found mostly feeding intolerance in 16 (22.2%) subjects examples: bleeding from OGT, abdominal distention in 8 (11.1%) subjects, vomitus in 5 (6.9%) subjects, and babies vomitus, abdominal distention, or bleeding from OGT in each 3 (4.2%) subjects.

This study found that NEC can occur in preterm babies early feeding. (Panigrahi *et al.*, 1994) Respons immature gen innate immune in NEC caused severe inflammation respons in bowel preterm babies (Nanthakumar *et al.*, 2011). The study in IUGR babies found that insidens NEC do not change in early or latest feeding about 15% and 18% with RR 1.2 (95% CI:0.77-1.87). Incidence jaundice caused cholestasis, and improved discharge from hospital (Leaf *et al.*, 2012). The study RCT quote by Dutta *et al.*, found that similar insidens NEC with  $p=0.76$ , but the earlier feeding babies decreased length of stay (LOS) in NICU with  $p=0.28$ .

In this study it is found only one baby who born from the mother with UA reverse end-diastolic flow with gestational age less than 32 weeks. This baby is dead before full feed. From nine babies with UA mothers absent end-diastolik flow, two babies are not feeding at all with gestational age less than 32

weeks, three babies gave minimal enteral feeding (MEF) but infection after that, and feeding intolerance (two babies 32 weeks gestational age and 1 baby 34 weeks gestational age). The fifth babies died. From nine babies, three babies full feed before 14 days and 1 baby full feed after 26 days. So, we must careful feeding the babies with the UA reverse end-diastolic flow and absent end-diastolic flow, gestational age  $\leq 32$  weeks, and infections.

Bivariate data from the mother and the babies associated with full feed can analyzed to multivariate analysis. The data with  $p < 0.25$  such as gestational age, birth weight, clinical intolerance, radiological finding, and infections. Multivariate analysis with logistic regression found only 2 variables that predictors to feeding achievement gestational ages  $> 32$  weeks and the absence of clinical feeding intolerance with Odds ratio  $> 1$ . Infections with value  $p > 0.05$ , so infections can't be the predictors of feeding achievement. The research in Italia with retrospective cohort, from the 1864 very low birth weight babies, the predictor of late feeding achievement are less gestational ages, exclusive breastfeeding, CRIB II is high, hypertension mothers, Delivery with C-section, IUGR, and PDA. (Corvaglia *et al.*, 2014).

This study found that data distribution not normal, so we do not use mean or deviation standard. We use median and interquartile range. Minimal enteral feeding with median 2 days, range 0-4 days. This the same with study quote Adamkin DH found that the babies can start enteral feeding within 5 days (Adamkin, 2009). The babies can full feed with median 9.5 days. The babies can full feed between 3.3-15.5 days. In this study mostly babies fullfeed more than 14 days (2 weeks) in 45 (62.5%) babies. In 33 (45.8%) babies with gestational ages  $\leq 32$  weeks and the babies  $> 32$  weeks in 12 (16.7%) babies. Full feed limit is  $\leq 2$  weeks (14 days), that only 37 (51.4%) babies can full feed  $\leq 2$  weeks and of whom mostly never achieved full feed. Time to initiate MEF varied from the first day of life to the 21st day of life. Time to achieve full feed also varied from 3 days to 39 days. The most frequently used enteral feeding was a combination of breast milk and formula milk.

In this study, gestational age, birth weight, infection, feeding intolerance, and radiologic finding were associated with feeding achievement. Predictors of feeding achievement were gestational age  $> 32$  weeks and the absence of clinical feeding intolerance. The median of full feeding achievement

time was 9.5 days, which ranged from 3.5 to 15.5 days.

## CONCLUSION

A prospective study evaluating feeding intolerance with a different method, for example measuring mesenteric blood flow, should be conducted. In addition, multi center research is essential to improve the accuracy in predicting factors that influence feeding achievement. The result of this study can be used as guidance for health practitioners as careful attention should be given while providing enteral feeding to babies born with a gestational age  $< 32$  weeks, with a history of feeding intolerance, born from mother with preeclampsia in which reverse end-diastolic flow and absent end-diastolic flow were present.

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