Cognitive outcome in late preterm babies

Ayu Setyorini¹, Soetjiningsih¹, Ekawaty L. Haksari²

Abstract

Background Late preterm babies are at risk for delayed cognitive outcome, but little attention has been paid on this issue. There has been a general assumption that this group of babies will have the same development as full-term babies.

Objective To compare the cognitive development between late preterm babies and full-term babies.

Methods A prospective cohort study was conducted at the Department of Child Health Medical School of Udayana University/Sanglah Hospital. Babies with 34 to 42 weeks of gestational age who were born in Sanglah Hospital between November 1st 2007 and December 31st 2008, were recruited to the study. Cognitive development of each baby was measured by Mullen Scale’s of Early Learning twice, at 7 days and 3 months of age. We used corrected age for late preterm babies and chronological age for full-term babies.

Results The incidence of under-average development for late preterm babies at three months corrected age was 47.8% compared to 4.1% among fullterm babies (P < 0.0001). The relative risk for under-average development among late preterm babies was 11.8 (95%CI 9.95 to 13.75). Multivariate analysis revealed late preterm influenced cognitive significantly with OR 17.01 (95%CI 1.15 to 32.87).

Conclusions Cognitive outcome of late preterm babies was delayed compared to full-term babies. [Paediatr Indones. 2010;50:239-244].

Keywords: cognitive outcome, late preterm babies, Mullen Scale of Early Learning

Late preterm babies, who are born within 34 to < 37 weeks of gestational age (GA), are at risk for deterioration because of organ immaturity, medical intervention and its complications, and the effect of condition that cause the prematurity.¹ One of the important effect of the deteriorations is delayed cognitive outcome of survived preterm babies.²⁻⁷ Most of the studies on cognitive outcome of preterm babies were conducted on high risk preterm baby group.⁸⁻¹³ Only few studies were conducted on late preterm babies even though this subgroup constituted 70% of the survived preterm babies.¹⁴⁻¹⁶ This subgroup also had a little attention in the following observation because of general assumption that this group had a little risk to develop abnormally.¹⁷

Intervention for delayed development would have the best result, if conducted as early as possible. One study in Bali reported that stimulation for low birth weight infant already showed result at three
months corrected age. Based on this, we conducted our study to compare cognitive outcome between late preterm and full-term babies at three months corrected age.

**Methods**

This was a prospective cohort study on babies born within 34 to 42 weeks of gestational age, in Sanglah Hospital between November 1st 2007 and December 31st 2008. Inclusion criteria were singleton with birth weight appropriate to gestational age, mother aged 20 to 35 years, and live permanently in Denpasar. Exclusion criteria were major anomaly congenital, severe asphyxia, traumatic delivery at head region, early neonatal complication (convulsion, apnea, hyperbilirubinemia, hypoglicemia, respiratory distress). Drop out criteria were clinically sepsis or positive microorganism in blood culture, severe head trauma, and death before the end of the study. The babies were recruited by consecutive sampling. Written informed consent was asked from parent/guardian of every baby who met the eligibility criteria within 48 hours after birth. Measurement of gestational age were performed using Dubowitz score, birthweight (BW) with DS Pediatric Examining Table produced by Atom Medical Corp., head circumference (HC) with plastic tape, and blood glucose (Optium Xceed). Some demographic data such as parent’s education, family income, the number of family members were collected by questionnaire.

By the age of seven days, parents were asked to take their babies to children outpatient clinic at Sanglah Hospital. History taking and physical examination were conducted to identify any signs of early neonatal complications. Babies who had any clinical sign of early neonatal complication were turned out from the study. Cognitive outcome of was measured using Mullen Scale of Early Learning (MSEL).

At three months of age, corrected age for late preterm babies and chronological age for fullterm babies, data about babies’ intake, caretaker and education were collected by history taking to the parent. We also measured the weight, length, HC, and cognitive development with MSEL. MSEL measures cognitive development from five different domains: gross and fine motoric, visual receptive, receptive and expressive language; and it can be used largely to diagnose developmental delay in our setting. The measurement was conducted by two research assistants with an interobserver agreement of 0.67. The doctor and the research assistants were blinded. The doctor did not know the result of cognitive measurement and the assistants did not know whether the baby was late preterm or full-term. At the end of sampling, the whole data were analyzed by computer program. Ethical approval of this study was obtained from Research and Development Committee of Faculty of Medicine, Udayana University, Denpasar.

The gestational age was determined in weeks, based on Dubowitz score. Late preterm was defined as gestational age of 34 to < 37 weeks and full-term as 37 to 42 weeks. Cognitive outcome was a composite standard score (CSS) appropriate with MSEL and divided into two categories: a) average if CSS was 85 to 115 and b) below average if CSS was less than 85. Nutritional status at 3 m.o was assessed based on WHO Z score of weight to length calculated. It was defined as normal if the Z score within -2 to +2 standard deviation (SD) and as malnutrition if the Z score was < -2 SD. Family income was assessed based on parent’s report. It was considered as adequate if the income was more than minimum regional income of Bali Province year 2007 to 2008 and not adequate if less than that.

Numerical data was analyzed by independent t-test if the distribution was normal and Mann-Whitney test if the distribution was not normal. Categorical data was analyzed by chi-square test. Multivariate analysis with stepwise logistic regression was done to identify the association between gestational age and cognitive outcome.

**Results**

During the period of November 1st 2007 to December 31st 2008 there were 161 babies who met the inclusion criteria. Thirteen of them were excluded because of neonatal sepsis and five babies were lost to follow up. The total subject until the end of the study was 143 babies, consisted of 69 late preterm and 74 fullterm babies.

The baseline characteristics of two groups were
similar, except for birthweight and weight at 3 months of age (Table 1).

The cognitive outcome based on MSEL is presented in Table 2. Late preterm babies were more common to have the result of MSEL of below average than that in full-term babies, both at 7 days and 3 months of age. The relative risk of below average cognitive development in late preterm babies was 11.8 (95% CI 9.95 to 13.75).

The mean CSS of late preterm babies was lower than that of full-term babies (Table 3). However, the developmental rate which is the different CSS between 7 days and 3 months of age was not different, both in the late preterm and full-term babies.

Delayed development was occurred in all developmental domain as reflected by lesser t-score of each developmental domain in the late preterm babies (Table 4).

A proportion of late preterm babies experienced development category alteration from below average to average which was not occured in fullterm babies (Table 5).

---

Table 1. Characteristics of late preterm and fullterm groups

| Characteristic                  | Late preterm (n = 69) | Fullterm (n = 74) |
|-------------------------------|-----------------------|-------------------|
| Birthweight, g, median (range) | 2500 (1900 to 2500)   | 3175 (2600 to 4000) |
| Head circumference, cm, median (range) | 32 (29 to 34)       | 33 (30 to 38)   |
| Weight at 3 m.o, g, median (range) | 6100 (5000 to 7700)  | 6800 (5000 to 8000) |
| Head circumference at 3 m.o, cm, median (range) | 39 (33 to 46)       | 40 (37 to 43)   |
| Male (%)                      | 40 (58)               | 40 (54)           |
| malnutrition at 3 month (%)   | 2 (2.9)               | 1 (0.4)           |
| Father’s education, (%)       |                       |                   |
| Elementary school             | 8 (11)                | 3 (4)             |
| Junior high school            | 16 (23)               | 15 (20)           |
| Senior high school            | 38 (55)               | 46 (62)           |
| Academician degree-holder     | 7 (10)                | 10 (13)           |
| Mother’s education, (%)       |                       |                   |
| Elementary school             | 12 (17)               | 10 (13)           |
| Junior high school            | 23 (33)               | 16 (21)           |
| Senior high school            | 31 (44)               | 43 (58)           |
| Academician degree-holder     | 3 (4)                 | 5 (6)             |
| Adequate family income (%)    | 42 (60)               | 49 (66)           |
| Breastfed within 3 mo (%)     | 40 (58)               | 39 (52)           |
| Cared by parent (%)           | 58 (84)               | 5 (74)            |
| Caretaker’s education (%)     |                       |                   |
| Elementary school             | 18 (26)               | 21 (28)           |
| Junior high school            | 24 (34)               | 23 (31)           |
| Senior high school            | 26 (37)               | 28 (37)           |
| Academician degree-holder     | 1 (1)                 | 2 (2)             |

Table 2. MSEL descriptive category in late preterm and full-term babies

| Age        | Gestational age | Mullen Scale Descriptive Category | Total | RR   | 95% CI  | P     |
|------------|-----------------|-----------------------------------|-------|------|--------|-------|
|            | Below average   | Average                           |       |      |        |       |
| 7 d.o      | Late preterm, n (%) | 51 (74)          | 18 (26) | 69   | 18.23  | 15.33 to 21.24 | <0.0001 ¶ |
|            | Fullterm, n (%)  | 3 (4)                          | 71 (96) | 74   |        |       |
| 3 m.o      | Late preterm, n (%) | 33 (48)          | 36 (52) | 69   | 11.80  | 9.95 to 13.75  | <0.0001 ¶ |
|            | Fullterm, n (%)  | 3 (4)                          | 71 (96) | 74   |        |       |

¶ x² test
Stepwise regression logistic found that cognitive outcome was influenced by gestational age and weight (Table 6).

**Discussion**

Late preterm infants are the largest survivors among preterm infants. These survivors are at risk of developmental delay. A study reported that delayed development of late preterm babies was 36% higher than that of fullterm babies. Other study reported that one third proportion of babies born within 32 to 35 weeks GA would have learning problem at school age. Neuronal maturation started early in embryonal phase until few years after the baby born. There are several critical periods in brain development which need normal and healthy environment as well as enough time to produce normal brain. The cortical brain volume increases five time within 35 to 41 weeks GA. At 34 weeks of GA, total brain weight was 65% of fullterm babies and cortical volume was 55%. This fact placed 34 to 37 weeks GA as a critical period for brain development and maturation. Other possible reason is neuron subplate was not formed yet before 36 weeks GA. An optimal neuron subplate was needed for continuity of axon from thalamus to higher cortical level.

Development tasks for 7 days old babies are very few and could not be used as a predictor for cognitive development at later age. Large proportion of late preterm infants (26%) who progressed from below average to average cognitive development in this study proved that development was a dynamic process which was changed within time. Appropriate intervention plays a role to make a better achievement in shorter time.

### Table 3. Mean composite standard score of late preterm and fullterm babies

| Age     | Mean composite standard score (SD) | Mean difference (95%CI) | P     |
|---------|-----------------------------------|-------------------------|-------|
|         | Late preterm                      | Fullterm                |       |
| 7 d.o   | 83.2 (SD 3.5)                     | 87.8 (SD 1.2)           | 4.6 (3.7 to 5.4) | <0.0001† |
| 3 m.o   | 87.0 (SD 3.3)                     | 91.8 (SD 2.4)           | 4.6 (3.6 to 5.5) | <0.0001† |

† Mann-Whitney test

### Table 4. t-score of each developmental domain of MSEL for fullterm and late preterm babies at 3 months of age

| Developmental domain | Median t-score (range) | P     |
|----------------------|------------------------|-------|
|                      | Late preterm           | Fullterm |
| Gross motoric        | 37 (31 to 37)          | 37 (31 to 37) | 0.01 |
| Fine motoric         | 34 (28 to 34)          | 34 (34 to 34) | <0.0001 |
| Receptive visual     | 26 (20 to 40)          | 40 (20 to 40) | 0.03 |
| Receptive language   | 35 (27 to 35)          | 35 (35 to 35) | 0.03 |
| Expressive language  | 41 (31 to 41)          | 41 (41 to 41) | 0.03 |

### Table 5. Alteration category of development late preterm and fullterm babies at 7 d.o and 3 m.o

| Gestational age | Proportion which experienced alteration from below average to average category | P     |
|-----------------|-----------------------------------------------------------------------------|-------|
|                 | Changed | Not changed |                                           |
| Late preterm, n(%) | 18 (26) | 51 (74) | <0.0001 |
| Fullterm, n(%)    | 0 (0)   | 74 (100) |                                           |

### Table 6. Multivariate analysis (logistic regression) of factors associated with below-average cognitive outcome at 3 months corrected age

| Variable     | OR    | 95%CI       | P     |
|--------------|-------|-------------|-------|
| Late preterm | 17.01 | 1.15 to 34.87 | 0.03 |
| Low birthweight | 1.00 | 1.00 to 1.03 | <0.0001 |
| Weight at 3 m.o | 1.00 | 1.00 to 1.01 | <0.0001 |
This study found that delayed development in late preterm infants occurred in all aspects of developmental domain. Fewer gross motoric ability would place a child to fewer chance for environmental exploration and movement variation. Visual disturbance would blocked a child to receive visual stimulation which would affect reading ability. Several studies found deficit in language development which was similar to our study. Deficit in language development would rise the risk of learning difficulties at school age. "Delayed development could be detected as early as 3 months of age. However, the very short observational time in this study limits us to report the impact of GA to cognitive outcome at school age. In addition, we could not identify the etiology of prematurity which lead to inability to associate it with the cognitive outcome. Brain traumatic injury was assumed from mode of delivery and not by head ultrasonography because this kind of measurement was not routinely done in our setting. Our study also could not define the quality of stimulation that was already given at home for our subjects. The result of this study emphasized on risk of delayed development in late preterm babies. It would be better to make a longterm follow up to late preterm babies. We should advice the parents to do more warm and responsive caregiving for the late preterm babies, and to start stimulation immediately because this might affect cognitive outcome."

We conclude that cognitive outcome of late preterm babies is delayed in all aspects of developmental domain compared to fullterm babies. A longterm evaluation of child developmental should have been started as soon as 3 months of age, which will give a benefit for the parents and the babies.

References
1. Engle WA, Tomashek KM, Wallman C. “Late-preterm” infants: a population at risk. Pediatr. 2007;120:1390-401.
2. Aylward GP. Cognitive function in preterm infants, no simple answers. JAMA. 2005;292:673.
3. Colvin M, McGuire W, Fowlie PW. Neurodevelopmental outcomes after preterm birth. Br Med J. 2004;329:1390-3.
4. Pierrehumbert B, Nicole A, Muller-Nix C, Forcada-Guex M, Ansermet F. Parental post-traumatic reactions after premature birth: implications for sleeping and eating problems in the infant. Arch Dis Child Fetal Neonatal Ed. 2003;88:F400-4.
5. Soetjiningih. Tumbuh-kembang anak. In: Ranuh IGNG, editor. Tumbuh kembang anak. 2nd ed. Jakarta: EGC, 1998; p. 1-36.
6. Vohr BR, O'Shea M, Wright LL. Longitudinal multicenter follow-up of high-risk infants: why, who, when, and what to assess. Semin Perinatol. 2003;27:333-42.
7. Wolke D. Psychological development of prematurely born children. Arch Dis Child. 1998;78:567-70.
8. Takahashi S, Endo A, Minato M. Why do we help a micropreemie to live? Acta Pædiatr. 2003;92:773-5.
9. Cooke RWI. Perinatal and postnatal factors in very preterm infants and subsequent cognitive and motor abilities. Arch Dis Child Fetal Neonatal Ed. 2005;90:60-3.
10. Evans DJ, Levene MI. Evidence of selection bias in preterm survival studies: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2003;88:F199-202.
11. Macfarlane PL, Wood S, Bennett J. Non-viable delivery at 20-23 weeks gestation: observations and signs of life after birth. Arch Dis Child Fetal Neonatal Ed. 2003;88:F199-202.
12. McAnaliffe CM, Wallace IF, Vahoughan HG. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. Pediatr. 1996;98:1167-78.
13. Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA. 2000;284:1939-47.
14. Guinn D, Gibbs R. Infection-related preterm birth: a review
of the evidence. NeoReviews. 2002;3:e86-95.
15. Kramer MS, Demissie K, Yang H, Platt RW, Sauvé R, Liston R. The contribution of mild to moderate preterm birth to infant mortality. JAMA. 2000;284:843-9.
16. Slattery MM., Morrison JJ. Preterm delivery. Lancet. 2002;360:1489-97.
17. Morse SB, Zheng H, Tang Y, Roth J. Early school-age outcomes of late preterm infants. Pediatr. 2009;123:e622-9.
18. Windiani IGAT. Dampak stimulasi dini terhadap perkembangan bayi berat badan lahir rendah sesuai masa kehamilan pada umur koreksi 3 bulan [thesis]. Denpasar: Fakultas Kedokteran Universitas Udayana; 2004.
19. Haddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32–35 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001;85:F23-8.
20. Kalia JL, Visintainer P, Brumberg HL, Pici M, Kase J. Comparison of enrolment in interventional therapies between late-preterm. Pediatr. 2009;123:804-9.
21. Billiards SS, Pierson CR, Haynes RL, Folkert RD, Kinney HC. Is the late preterm infant more vulnerable to gray matter injury than the term infant. Clin Perinatol. 2006;33:915-33.
22. Fallang B, Hadders-Algra M. Postural behaviour in children born preterm. Neural Plast. 2005;12:175-82.
23. Goyen T, Lui K, Woods R. Visual-motor, visual-perceptual, and fine motor outcomes in very low birth weight children at 5 years. Developmental Medicine and Child Neurology. 1998 ;40:76-81.
24. Gabbard C, Goncalves VMG, Santoa DCC. Visual-motor integration problems in low birth weight children. J of Clinical Psychology in Medical Settings. 2001;8:199-204.
25. Ylherva A, Olsen P, Maki-Torkko E, Koiranen M, Jarvelin MR. Linguistic and motor abilities of low-birth weight children as assessed by parents and teachers at 8 years of age. Acta Paediatr. 2001;90:1440-9.
26. Nelson HD, Nygren P, Walker M, Panoscha R. Screening for speech and language delay in preschool children: systematic evidence review for the US preventive service task force. Pediatr. 2006;117:e298-319.
27. Hohm E, Jennen-Steinmetz C, Schmidt MH, Laucht M. Language development at ten months, predictive of language outcome and school achievement ten years later? Eur Child Adolesc Psychiatry. 2007;16:149-56.
28. Kirkegaard I, Obel C, Hedegaard M, Henriksen TB. Gestational age and birth weight in relation to school performance of 10-year-old children: a follow-up study of children born after 32 completed weeks. Pediatr. 2006;118:1600-6.
29. Gale CR, O’Callaghan FJO, Godfrey KM, Law CM, Martyn CN. Critical periods of brain growth and cognitive function in children. Brain. 2004;127:321-9.
30. Cheong JLY, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatr. 2008;121:e1534-40.
31. Shenkin SD, Starr JM, Pattie A, Rush MA, Whalley LJ. Birth weight and cognitive function at age 11 years: the Scottish mental survey 1932. Arch Dis Child. 2001;85:189-97.
32. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008;359:262-73.
33. Whitaker AH, Feldman JF, Lorenz JM, McNicholas F, Nieto M, McCulloch D, et al. Motor and cognitive outcomes in non-disabled low-birth-weight adolescents, early determinants. Arch Pediatr Adolesc Med. 2006;160:1040-6.
34. Dina D. Kejadian dan faktor risiko penyimpangan perkembangan pada bayi berat badan lahir rendah di RSUP Sanglah Denpasar [thesis]. Denpasar: Fakultas Kedokteran Universitas Udayana; 1996.
35. Gray RF, Indurkhya A, McCormick MC. Prevalence, stability, and predictors of clinically significant behavior problems in low birth weight children at 3, 5, and 8 years of age. Pediatr. 2004;114:736-43.
36. Van Baar AL, Vermaas J, Knots E, de Kleine MJK, Soons P. Functioning at school age of moderately preterm children born at 32 to 36 weeks gestational age. Pediatr. 2009;124:251-7.
37. Petrini JR, McCormick MC, Massolo M, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr. 2009;154:169-76.
38. Adams-Chapman I. Neurodevelopmental outcome of the late preterm infant. Clin Perinatol. 2006;33:947-64.
39. Reuner G, Hassenplug A, Pietz J, Philippi H. Long-term development of low-risk low birth weight preterm born infants: neurodevelopmental aspects from childhood to late adolescence. Early Hum Dev. 2009;85:409-13.
40. Smith EK, Landry SH, Swank PR. The role of early maternal responsiveness in supporting school-aged cognitive development for children who vary in birth status. Pediatr. 2006;117;1608-17.