Neonatal Morbidity in Late Preterm Infants Associated with Intrauterine Growth Restriction

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Abstract

AIM: This study aims to compare the neonatal morbidity of Intrauterine growth restricted (IUGR) Late Preterm (LP) babies, to those born Late Preterm but evaluated as Appropriate for Gestational Age (AGA).

METHODS: The study is a 2-year prospective one that used data from the Neonatal Intensive Care Unit (NICU) charts of LP neonates born in our tertiary maternity hospital “Koço Gliozheni” in Tirana. Congenital anomalies and genetical syndromes are excluded. Neonatal morbidity of IUGR Late Preterm is compared to those born Late Preterm but evaluated as AGA. OR and CI, 95% is calculated.

RESULTS: Out of 336 LP babies treated in NICU, 88 resulted with IUGR and 206 AGA used as a control group. We found significantly higher morbidity in the IUGR group for hypoglycemia, polycythemia, feeding intolerance, birth asphyxia and seizures, secondary sepsis have higher morbidity but the difference is not significant. No differences were found for hyperbilirubinemia in both groups. No neonatal deaths were observed in both groups.

CONCLUSION: Our study showed that late preterm IUGR has a significantly higher risk for neonatal morbidity when compared to late preterm AGA babies.

Introduction

Late preterm birth is defined as birth between 34 0/7 weeks and 36 6/7 weeks of gestation [2]. They are the fastest-growing in the preterm group in the last decade. In the United States in 2005, LP births account for more than 70% of all preterm births [15]. The number increased from 10.9% in 1990 in 12.8% in 2007 [3]. Now it is known that in the late preterm infants, the morbidity and mortality are higher than in term neonates. In Albania, there are no official data published about the late preterm birth rate and their morbidity and mortality.

IUGR is the term used to designate a fetus that has not reached its potential growth [1]. Intrauterine growth restriction is one of the causes of the late preterm delivery, and it occurs more often in late preterm infants than term ones. IUGR itself is associated with perinatal morbidities and contributes to increased metabolic disease and poor neurodevelopmental outcome.

IUGR is an important cause of high-risk pregnancies and elective preterm deliveries. IUGR is present only in a small percentage of deliveries, but an increased frequency has been observed among women who go into preterm labour followed by premature delivery. Preterm infants and with intrauterine growth restriction are vulnerable to the complications of prematurity and IUGR as well, though there are conflicting findings in the literature about late preterm IUGR and AGA morbidity [7]. It appears normal, unchanged in the IUGR group compared to AGA LP infants [5] suggesting an advantage to the stress of poor growth.

The objective of this study is to compare...
neonatal morbidity between late preterm IUGR and AGA infants with the same gestational age to better understand the neonatal outcomes of these infants for both complications of IUGR and prematurity.

**Methods**

Our study analysed the prospectively gathered data of babies born late preterm in two years from January 2014 – December 2015 in our tertiary maternity hospital “Koço Gliozheni” in Tirana. We analysed the data from medical charts of late preterm infants born in our hospital who entered NICU and compared the morbidity of IUGR LP, with the AGA as a control group. Gestational age at delivery was determined by mothers last menstrual period and or confirmed by early ultrasound examination. The evaluation of IUGR is done by calculating 3 growth indexes (Ponderal Index, that is an index of weight-related to length; the ratio of Head Circumference to Abdominal Circumference (HC/AC); and the difference between Chest Circumference with Abdominal Circumference ≥ 3 cm) after anthropometric measurements in the respective charts. In case 2 or more indexes result not normal the baby is identified as IUGR. AGA are babies whose birth weight is above the 11th to 89th percentile of birth weight in the growth curve of Alexander et al., [14]. Pregnancies with congenital anomalies or with unknown data criteria were excluded. Delivery characteristics included gestational age at birth, route of delivery, birth, apgar scores. Neonatal data included respiratory morbidity with, (transient tachypnea of the newborn and respiratory distress), neonatal sepsis, sepsis follow up, birth depression with Apgar score < 7 the 5th minute, seizures and metabolic disorders as hyperbilirubinemia, hypoglycemia, polycythemia, and feeding intolerance [8]. Diagnosis and treatments are done by using the NICU protocol for every disorder and the criteria outlined in Standard Textbooks of Neonatology.

Hypoglycemia: defined as a blood glucose level less than 40 mg/dl in the first 24 hours and less than 45 mg/dl after 24 hours.

Hyperbilirubinemia: Clinically visible jaundice requiring phototherapy or exchange transfusion as per hour specific total serum bilirubin nomogram (AAP chart) [19].

Sepsis :Probable sepsis :positive septic screen (two of the five parameters, total white blood count < 5000/mm³ or > 15000/mm³, immature to total polymorph ratio ≥ 0.2, absolute neutrophil count less than 1750/mm³ or > 7200/mm³, C reactive protein > 1 mg/dl, platelets < 100.000/mm³), and proven sepsis: Isolation of pathogens from blood or Cerebrospinal fluid [17], [18].

Feeding intolerance: Inability to digest enteral feedings associated with increased gastric residuals, abdominal distension and or emesis, often leading to a disruption of the feeding plan.

Polycythemia: Hematocrit or haemoglobin concentration > 2 SD above the normal value for gestational and postnatal age associated with clinical findings resulting from hyperviscosity [16].

Statistical data were collected into the database. The difference in morbidity between two groups is compared by calculating the OR and confidence interval 95% using the Fisher exact test for statistical analysis. The result is considered significant at p < 0.05.

**Results**

During the 2-year study period, 1334 babies entered the NICU. Of those admissions, 336 or 25% were babies born late preterm i.e. 34 0/7 – 36 6/7 weeks of gestational age. 3 infants are excluded from the study as they were born with a congenital anomaly. IUGR late preterms treated in the NICU were 88 babies and AGA 206 babies.

Gestational age at delivery ranged from 34 to 36.9 weeks, with a median of 35.1 and did not differ between the two groups. Mode of delivery was 78% cesarean section in the IUGR group vs 50% in the AGA group with a significant difference. The length of stay of the newborn in the NICU differed significantly as well between the two groups (Table 1).

| Table 1: The length of stay of the newborn in the NICU | IUGR LP | AGA LP | OR | CI 95% |
|---|---|---|---|---|
| Median Gestational age | 35.1 | 35.07 | | |
| SD | ± 0.8 | ± 0.8 | | |
| Mode of delivery (CS) | 78% | 61% | 50% | 97% | 2.5 | 1.49-4.3 p = 0.002 |
| Length of NICU stay | 9.45 | 5.5 | | |
| Median weight | 2500.05 gr | 1871.9 gr | | |
| SD | ± 318.5 | ± 382.1 | | |

LP: late preterm; IUGR: intrauterine growth restricted; AGA: appropriate for gestational age.

The neonatal morbidity: we found a slight difference between the two groups as it concerns overall respiratory morbidity (Transient Tachypnea, Respiratory Distress Syndrome) where IUGR LP is less vulnerable to this morbidity compared to AGA LP. No difference was found about, hyperbilirubinemia and sepsis workup. We found a significant difference between the two groups about hypoglycemia, where IUGR LP suffer more than AGA. For polycythemia, feeding problems, birth depression Apgar score < 7, 5th minute of life, seizures and secondary sepsis IUGR LP are more vulnerable, but the difference is not significative (Table 2).
Discussion

Late preterm births are an increasing problem in the world nowadays. They account for 70% of all preterm births. They experience a higher incidence of neonatal morbidity and mortality compared to term neonates [7]. On the other hand, IUGR is a problem that complicates their prematurity situation, contributing to an increased morbidity and mortality observed among late preterms.

Although there is a lack of studies about IUGR late preterms, as in other studies, we found a slight difference for respiratory morbidity, probably this a contribution to their inutero stress that leads to an early pulmonary maturity and the high incidence of CS for AGA LP (50%). We did not observe severe complications as Necrotizing Enterocolitis NEC, Pulmonary Hemorrhage, and death perhaps because these are rare findings in this gestational group [15].

Problems like hypoglycemia, polycythemia and feeding intolerance are common in the IUGR preterm group, and neonatal sepsis is found more in this group rather than AGA because we did not exclude women with preterm premature rupture of membranes from our study [9]. As found in other studies Laptook and Jackson [20], hypoglycemia has an elevated incidence in late preterm infants as a result of deficient neoglycogenesis, hepatic glycogenolysis and hormonal irregularities. Finding seizures more often in IUGR group is linked to metabolic problems like hypoglycemia, but birth asphyxia as well, which is linked to the emergency of Cesarian Section interventions in IUGR Late Preterms in our hospital as a reference hospital in Albania.

Our study is focused on the early morbidity of late preterm infants, and we don’t have evidence about their long-term consequences in later life.

In conclusion, IUGR late preterm infants have higher morbidity compared to AGA LP, and IUGR is a major cause for late preterm delivery and CS delivery. A better understanding and evaluation of their problems is very important [12, [13].

Table 2: There are no deaths registered in either group

|                  | IUGR LP | AGA LP | CR | OR (95% CI) | p-value |
|------------------|---------|--------|----|-------------|---------|
| Respiratory Morbidity | 38.0%   | 33.0%  | 3.0 | 0.8-3.0     | 0.11    |
| Hyperbilirubinemia | 49.0%   | 42.0%  | 3.0 | 0.8-3.0     | 0.51    |
| Apgar score ≤ 7 in 5th min | 6.0%    | 3.5%   | 1.0 | 0.99-1.0   | 0.0001  |
| Seizures          | 3.4%    | 2.0%   | 1.0 | 0.99-1.0   | 0.0001  |
| Hypoglycemia      | 10.0%   | 4.0%   | 3.0 | 0.8-3.0     | 0.0001  |
| Polycythemia      | 3.0%    | 1.0%   | 1.0 | 0.99-1.0   | 0.0001  |
| Feeding problems  | 2.2%    | 1.0%   | 1.0 | 0.99-1.0   | 0.0001  |
| Neonatal sepsis   | 3.0%    | 1.0%   | 1.0 | 0.99-1.0   | 0.0001  |

LP: late preterm; IUGR: intrauterine growth-restricted; AGA: appropriate for gestational age.

References

1. Battaglia FC, Lubchenko LO. A practical classification of newborn infants by weight and gestational age. The Journal of pediatrics. 1967; 71(2):159-63. https://doi.org/10.1016/S0022-3476(67)80066-0
2. Engle WA. A recommendation for the definition of "late preterm" (near-term) and the birth weight-gestational age classification system. Seminars in Perinatology. 2006; 30(1):2-7. https://doi.org/10.1053/j.semperi.2006.01.002 PMid:16549206
3. Davidoff MJ, Dias T, Damus K, et al. Changes in the gestational age distribution among U.S. singleton births: impact on rates of late preterm birth, 1992 to 2002. Seminars in Perinatology. 2006; 30(1):8-15. https://doi.org/10.1053/j.semperi.2006.01.009 PMid:16549207
4. Dobson PC, Abell DA, Beischer NA. Mortality and morbidity of fetal growth retardation. Australian and New Zealand Journal of Obstetrics and Gynaecology. 1981; 21(2):69-72. https://doi.org/10.1111/j.1479-8288.1981.tb00781.x PMid:6945852
5. Clausesson B, Cnattingius S, Axelsson O. Preterm and term births of small for gestational age infants: a population-based study of risk factors among nulliparous women. British Journal of Obstetrics and Gynaecology. 1998; 105(9):1011-1017. https://doi.org/10.1111/j.1475-0325.1998.tb10266.x PMid:9763054
6. Teber AJ, Walterh FJ, Pena IC. Morbidity, mortality, and outcome of the small-for-gestational age infant. Seminars in Perinatology. 1988; 12(1):84-94.
7. McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstetrics and Gynecology. 2008; 111(1):35-41. https://doi.org/10.1097/01.AOG.0000297311.33046.73 PMid:18165390
8. Seubert DE, Stetzer BP, Wolfe HM, Treadwell MC. Delivery of the marginally preterm infant: what are the minor morbidities?. American journal of obstetrics and gynecology. 1999; 181(5):1087-91. https://doi.org/10.1016/S0002-9378(99)00706-4
9. Arnon S, Dolfin T, Litmanovitz I, Regev R, Bauer S, Feigin M. Preterm labour at 34-36 weeks of gestation: should it be arrested?. Paediatric and perinatal epidemiology. 2001; 15(3):252-6. https://doi.org/10.1046/j.1365-3016.2001.00057.x PMid:11489153
10. Gladstone IM, Katz VL. The morbidity of the 34-to 35-week gestation: should we reexamine the paradigm? American journal of perinatology. 2004; 21(01):9-13. https://doi.org/10.1055/s-2004-820503 PMid:15017476
11. Bhutani VK, Johnson L. Kernicterus in late preterm infants cared for as term healthy infants," Seminars in Perinatology. 2006; 30(2):89-97. https://doi.org/10.1053/j.semperi.2006.04.001 PMid:16731293
12. Shapiro-Mendoza CK, Tomashke KM, Kotelchuck M, Barfield W, Weiss J, Evans S. Risk factors for neonatal morbidity and mortality among "healthy," late preterm newborns. Seminars in Perinatology. 2006; 30(2):54-60. https://doi.org/10.1053/j.semperi.2006.02.002 PMid:16731277
13. Raja TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics. 2006; 118(3):1207-14. https://doi.org/10.1542/peds.2006-0018 PMid:16951017
14. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstetrics & Gynecology. 1996; 87(2):163-8. https://doi.org/10.1016/0029-7844(95)00386-X
15. March of Dimes Perinatal Data Center, "Late preterm birth: every week matters. 2005," National Center for Health Statistics, final natality data, January 2008, http://www.marchofdimes.com/peristats/
16. Oski FA, Naiman JL. Polycythemia and hyperviscosity in the neonatal period. In: Hematologic Problems in the Newborn, 3 ed, Oski FA (Ed), WB Saunders, New York, 1982:87.

17. Edwards MS, Baker CJ. Sepsis in the newborn, p 545-561 In Gershon AA, Hotz PJ, Katz SL, editors. (ed), Krugman's infectious diseases of children, 11th ed. Mosby, Philadelphia, PA, 2004.

18. Manroe BL, Weinberg AG, Rosenthal CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J. Pediatr. 1979; 95:89-98.

19. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics. 2001; 108:31-9. https://doi.org/10.1542/peds.108.1.31 PMid:11433051

20. Laptook A, Jackson GL. Cold stress and hypoglycemia in the late preterm (“near-term”) infant: impact on nursery of admission. Seminars in Perinatology. 2006; 30(1):24-27. https://doi.org/10.1053/j.semperi.2006.01.014 PMid:16549210