Medicina Universitaria. 2016;18(70):3–9

MEDICINA UNIVERSITARIA

www.elsevier.es/rmuanl

ORIGINAL ARTICLE

Risk factors and the relation of lactic acid to neonatal mortality in the first week of life

I. Rodríguez-Balderrama*, P.J. Ostia-Garza, R.D. Villarreal-Parra, M. Tijerina-Guajardo

Neonatology Service at the ''Dr. José Eleuterio González'' University Hospital of the Autonomous University of Nuevo León in Monterrey, Nuevo León, Mexico

Received 19 August 2015; accepted 17 December 2015
Available online 8 May 2016

KEYWORDS
Lactic acid;
Neonatal mortality;
Preterm;
Mechanical ventilation;
Mexico

Abstract

Objective: To determine the relationship between lactic acid levels and neonatal mortality in the first week of life, in patients admitted to the Neonatal Intensive Care Unit (NICU) of the ''Dr. José E. González'' University Hospital.

Material and methods: Prospective, observational and diagnostic test performed in the neonatal ward of the ''Dr. José Eleuterio González'' University Hospital. We included all live preterm infants on mechanical ventilation who were admitted to the NICU from November 1, 2011 to October 31, 2012.

Results: One hundred and fifty four patients met the inclusion criteria. At 72 h, we found that the best sensitivity (95%) was when lactate was less than 1.5 mmol/l and the best specificity (89%) was present when lactate levels were greater than 2.5 mmol/l. The pH <7.25 had a sensitivity of 76% and specificity of 96%. At 168 h (7 days) we found that the best sensitivity (91%) was when lactate levels were less than 1.5 mmol/l, and that the best specificity (96%) was when lactate levels were greater than 2.5 mmol/l. We found that the pH <7.25 had a sensitivity of 36% and specificity of 91%.

Conclusion: The lactate serum, at 1.5 mmol/l, has a sensitivity (to be killed) of 95% on the third day and 91% on the seventh day. When the pH is greater than 7.25 there is a specificity (to be alive) of 96% on the third day and 91% on the seventh day. 67% of the dead were under 1500 g, and were 61% under 28 gestational weeks.

* Corresponding author at: Servicio de Neonatología del Hospital Universitario ''Dr. José Eleuterio González'' de la UANL, Avenida Francisco I Madero y Gonzalitos, s/n, Col. Mitras Centro, código postal 64460 Monterrey, N.L., Mexico.

E-mail address: irb442000@yahoo.com.mx (I. Rodríguez-Balderrama).

http://dx.doi.org/10.1016/j.rmu.2015.12.001

Introduction

Lactic acid is a terminal product of the anaerobic metabolism of glucose, and it is obtained by a reduction of pyruvic acid in a reaction catalyzed by the lactic dehydrogenase enzyme, where a dinucleotide adenine nicotinamide (NAD) coenzyme goes from its reduced form to its oxidized form.[1–3]

Under normal conditions, serum levels are at 2 mEq/L or lower. However, exercise can elevate it up to 4 mEq/L. Most lactate is efficiently eliminated by the liver and is utilized in gluconeogenesis or in the production of energy. When considerable increases in lactate serum numbers are produced, with a reduction in lactate to pyruvate metabolism conversion, metabolic acidosis occurs, which is usually severe and may lead to patient death.[4]

Lactic acid is increased in situations of tissue hypoxia–ischemia. Different studies conducted in adults,[5] as well as in children[6,7] and newborns,[8] have shown that in critical situations, lactic acid levels at the moment of the patient's admittance to the ICU and its evolution have a positive correlation with the risk of death.[9]

Lactic acid can increase for several causes other than tissue hypoxia. Within the context of the ICU, in order of frequency, amongst the most probable are those of hemodynamic causes,[10] which determine tissue hypoxia,[11] as in the case of sepsis, heart failure, shock (cardiogenic and septic) and multiple organ dysfunction.[11] Amongst the non-hemodynamic causes there are[12,13]: the use of biguanides in diabetic patients, the use of pharmaceuticals such as adrenalin and nitroprusside, seizures, intestinal infarction, or in general, patients with intestinal hypomotility, short bowels, thiamine deficiency, liver diseases in general, ethanol overdoses, methanol, salicylates and ethylene glycol.

Lactate has proven to be a good prognostic indicator in hospitalized adults and children[14,15] and different types of patients, including critical,[16–18] and surgical,[19] with sepsis[20,21] and trauma.[22,23] Its main advantage is how fast and easy its determination is, and its evolutionary prognosis capability.[24,25]

The objective of this study is to determine the relationship of lactic acid levels with neonatal mortality rates in the first week of life, in patients admitted to the Neonatal Intensive Care Unit at the ''Dr. Jose E. Gonzalez'' University Hospital, as well as to quantify neonatal mortality rate prevalence in the first week of life in relation to lactic acid levels, to know non-pathological and pathological maternal backgrounds, learn the newborn's characteristics, to identify the main in-hospital morbidities, document the main causes of associated death, and identify lactate levels associated and a higher mortality rate.

Materials and methods

A prospective, observational and diagnostic test was performed in the neonatal ward of the ''Dr. José Eleuterio González'' University Hospital of the Autonomous University of Nuevo León. We included all live preterm infants on mechanical ventilation who were admitted to the NICU within the period of November 1, 2011 to October 31, 2012. The study was approved by the University's Ethics Committee with the folio no. NE12-003.

Exclusion criteria included all live preterm infants who did not require mechanical ventilation admitted to the NICU between November 1, 2011 and October 31, 2012, patients transferred from other hospital units, and those who did not meet the requirements of the file.

Variables were the following: the evaluated newborns' characteristics were weight at birth, and were classified into <1000 g, 1001–1500 g, 1501–2500 g and 2501–4000 g categories. Also, gestational age was evaluated and classified according to the number of weeks of gestation as <28 weeks, 28–33 weeks, and 34–36 weeks of gestation. Trophism was evaluated and classified as adequate weight for gestational age and low weight for gestational age.[26] They were divided by male and female, according to gender, and were evaluated and classified according to their APGAR score at 5 min in 0–3, 4–6 and 7–10 points.

Within these variables, the study included pathological and non-pathological maternal family history: no family history, smoking, alcoholism, drug addiction and tattoos on the mothers of the newborns, the number of sexual partners was studied, divided into one, two, three or more. According to the mother's health during pregnancy, they were divided into healthy, or whether the mother presented an ailment, such as high blood pressure, infections, preeclampsia, eclampsia or gestational diabetes, among others. Also, it was determined whether or not the patients carried out proper prenatal care.

Additionally, the mothers' age was evaluated and divided as follows: under 18 years old, from 19 to 30 years old, and over 30 years old. They were divided into single, married and the consensual union, according to their marital status. Regarding schooling, the classifications were illiterate, elementary, junior high school, high school, and bachelor's degree. Also, a classification according to their occupation was made, dividing them as follows: housewife, worker and student. Among the evaluated variables were causes of in-hospital morbidity and mortality, from which the following pathologies were studied: hyaline membrane disease grades 1 through 4, pulmonary edema, meconium aspiration syndrome, septic shock, sepsis, extreme prematurity and perinatal asphyxia.

Lactate and pH were studied at 72 h (3 days), assessing sensitivity, specificity, positive predictive value and negative predictive value of lactate levels >1.5 mmol/l, 2 mmol/l and lactate at 2.5 mmol/l, as well as pH <7.25 and <7.30.

Similarly, lactate and pH were studied at 168 h (7 days), assessing sensitivity, specificity, positive predictive value and negative predictive value of lactate levels >1.5 mmol/l and 2 mmol/l and lactate at 2.5 mmol/l, as well as pH <7.25 and <7.30.

Qualitative variables were used in the statistical analysis. The chi square (non-parametric) tests were utilized to test the hypothesis. An alpha value of 0.05 was used and the null hypothesis was rejected when the critical value was under 0.05.

Sensitivity, specificity, and both positive and negative prediction values were determined with a 2×2 contingency chart where the predictive or independent variable was alive or dead and the outcome or dependent variables

Table 1 Newborn characteristics.

	Total	Alive ($n = 118$)	Dead ($n = 36$)	Value of p
Weight at birth (g)				
<1000	30	10 (8.4%)	20 (55.5%)	<0.001
1001–1500	43	39 (33%)	4 (11.1%)	<0.05
1501–2500	53	46 (38.9%)	7 (19.5)	<0.05
2501–4000	28	23 (19.7%)	5 (13.9%)	0.44
Gestational age (weeks) × *DS*				
<28 sdg	29	7 (6%)	22 (61%)	<0.001
28–33	68	59 (50%)	9 (25%)	<0.001
34–36	57	52 (44%)	5 (14%)	<0.05
Trophism				
PAEG	76	59 (50%)	17 (47%)	
PBEG	78	59 (50%)	19 (53%)	0.77
Gender				
Male	93	69 (58%)	24 (66%)	0.37
Female	61	49 (42%)	12 (34%)	
APGAR at 5 mins				
0–3	4	0	4 (11%)	
4–6	15	12 (11%)	3 (9%)	<0.01
7–10	135	106 (89%)	29 (80%)	

were lactate levels >1.5 mmol/l, 2 mmol/l and lactate at 2.5 mmol/l, as well as pH<7.25 and <7.30.

Results

Within the period of time outlined in this study, there were 2657 births. 363 (13.6%) of these were admitted to the NICU. Out of the 363 admitted to the NICU, 226 (67.2%) were premature. Out of the premature ones, 154 met the inclusion criteria, from which 36 died and 118 survived.

When comparing their weight at birth, we are able to find that there were more children under 1000 g in the dead group ($p < 0.001$) and there were more children between 1000 and 2500 g in the alive group ($p < 0.05$). Regarding gestational age, there were more children under 28 weeks of gestation in the dead group with ($p < 0.001$) and more children with a gestational age of 28–33 weeks of gestation ($p < 0.001$) and 34–36 weeks of gestation (<0.05) in the alive group. Concerning trophism and gender, both groups were similar (NS). When comparing APGAR scores, there were more dead children with a low APGAR ($p < 0.001$) (see Table 1).

When comparing non-pathological and pathological maternal history, we are able to find that there were more mothers without any history in the alive group ($p < 0.001$) and there was a greater link of alcoholism (<0.05), drug addiction (<0.05) and tattoos (<0.001) in mothers of those patients who died. Regarding the number of sexual partners, those with 3 or more sex partners were higher in the dead group (<0.05).

When comparing the mothers' health during pregnancy, results show that in the dead group there were more mothers with high blood pressure (<0.001) and gestational diabetes ($p < 0.05$) and the presence of infections, preeclampsia, eclampsia and other diseases was not significant (NS). Prenatal care was similar in both groups (NS) (see Table 2A).

When comparing associated maternal age, we are able to observe more mothers <18 years old in the dead group ($p < 0.01$) and more mothers between 19 and 30 years old ($p < 0.01$) in the alive group. Marital status was similar in both groups (NS). Regarding schooling, there were more children in the dead group whose mothers has completed high school ($p < 0.001$), whereas in the alive group elementary school was predominant ($p < 0.001$). There were more working mothers in the dead group ($p < 0.05$) (see Table 2B).

When comparing in-hospital morbidity and mortality causes, we are able to observe that there were more dead children with grade 3 and 4 hyaline membrane disease diagnosis ($p < 0.001$), septic shock ($p < 0.01$) and prematurity ($p < 0.001$). On the other hand, sepsis was higher in the alive group ($p < 0.05$). The presence of grade 1 and 2 HMD, pulmonary edema, meconium aspiration syndrome and perinatal asphyxia were not significant (NS) (see Table 3).

At 72 h, findings show the best sensitivity (95%) was when lactate was lower than 1.5 mmol/l and the best specificity (89%) was with lactate levels higher than 2.5 mmol/l; pH <7.25 had a sensibility of 76% and a specificity of 96% (see Table 4).

At 168 h (7 days), findings show the best sensitivity (91%) was when lactate was lower than 1.5 mmol/l and the best specificity (96%) was with lactate levels higher than 2.5 mmol/l; pH <7.25 had a sensibility of 36% and a specificity of 91% (see Table 5).

Discussion

Lactic acid is a terminal product of the anaerobic metabolism of glucose.[1–3] Under normal conditions serum

Table 2A Pathological and non-pathological maternal antecedents.

	Total	Alive (n = 118)	Dead (*n* = 36)	Value of *p*
Non-pathological antecedents				
None	119	104 (88%)	15 (42%)	<0.001
Smoking	13	7 (6%)	5 (14%)	0.10
Alcoholism	5	2 (2%)	3 (8%)	<0.05
Drug addiction	11	5 (4%)	6 (16%)	<0.05
Tattoos	7	0	7 (20%)	<0.001
Number of sexual partners				
One	148	115 (97%)	33 (92%)	
Two	4	3 (3%)	1 (2%)	<0.05
Three or more	2	0	2 (6%)	
Maternal health during pregnancy				
Healthy	115	92 (77%)	23 (64%)	0.089
Art. hypertension	8	2 (2%)	6 (17%)	<0.001
Infections	2	2 (2%)	0	0.88
Preeclampsia	12	9 (8%)	3 (9%)	0.43
Eclampsia	2	2 (2%)	0	0.88
Gestational diabetes	5	2 (2%)	3 (9%)	<0.05
Other	10	9 (8%)	1 (4%)	0.30
Prenatal control				
Yes	135	102 (85%)	33 (92%)	0.40
No	19	16 (14%)	3 (8%)	

levels are at 2 mEq/L or lower.[4] Lactic acid is increased in situations of tissue hypoxia–ischemia,[5–8] and its levels have a high correlation with mortality.[9–11] The causes which provoke an increase of lactic acid can be hemodynamic or non-hemodynamic.[12–25]

The number of premature births continues to increase in developed countries, as well as the related low weight, with an increased mortality rate for patients that weigh less than 1500 g.[27,28] Within the findings of our study, when comparing weight at birth, we found that there were more children that weighed less than 1000 g in the dead group.

A very important relation between a high number of deaths and a gestational age of 28–31 weeks has been reported in various studies, showing that they present a higher risk of complications and mortality during their time in the NICU.[28,29] Within our findings, upon comparison of

Table 2B Pathological and non-pathological maternal antecedents.

	Total	Alive (*n* = 118)	Dead (*n* = 36)	Value of *p*
Maternal age				
<18 years	22	12 (10%)	10 (28%)	<0.01
19–30 years	112	92 (78%)	20 (55%)	<0.01
Over 30 years	20	14 (11%)	6 (17%)	0.45
Marital status				
Single	77	58 (49%)	19 (53%)	0.70
Married	68	54 (45%)	14 (39%)	0.46
Free Union	9	6 (5%)	3 (8%)	0.46
Schooling				
Illiterate	2	2 (5%)	0	0.43
Elementary	35	26 (13%)	9 (25%)	0.71
Junior high	103	87 (74%)	16 (44%)	<0.001
Highschool	13	3 (7%)	10 (27%)	<0.001
Bachelor's	1	0	1 (4%)	0.069
Occupation				
Housewife	126	99 (84%)	27 (75%)	0.22
Worker	19	11 (9%)	8 (22%)	<0.05
Student	9	8 (7%)	1 (3%)	0.37

Table 3 Causes of intrahospital morbidity.

	Total	Alive (n = 118)	Dead (n = 36)	Value of p
HMD				
Degree 1 and 2	8	8 (7%)	0	0.10
Degree 3 and 4	89	76 (64%)	13 (36%)	<0.01
PE	8	8 (7%)	0	0.10
MAS	1	1 (0.9%)	0	0.57
Septic shock	2	0	2 (5.5%)	<0.01
Sepsis	12	12 (10%)	0	<0.05
Extreme prematurity	29	9 (7.5)	20 (56%)	<0.001
Perinatal asphyxia	5	4 (3.5%)	1 (2.5%)	0.85

Table 4 Lactate and pH of the patients at 72 h (3 days).

	Sensibility	Specificity	VPP	VPN
Lactate >1.5 mmol/l	95%	60%	35%	98%
Lactate >2 mmol/l	83%	76%	45%	95%
Lactate >2.5 mmol/l	75%	89%	62%	94%
pH >7.25	76%	96%	82%	94%
pH >7.30	29%	80%	24%	83%

Table 5 Lactate and ph of the patients at 168 h (7 days).

	Sensibility	Specificity	VPP	VPN
Lactate >1.5 mmol/l	91%	70%	35%	98%
Lactate >2 mmol/l	75%	85%	68%	89%
Lactate >2.5 mmol/l	52%	96%	86%	83%
pH >7.25	36%	91%	62%	78%
pH >7.30	22%	75%	93%	71%

gestational ages, we found that there were more children at less than 28 weeks ($p < 0.001$) in the dead group, and more children at 28–33 weeks and 34–36 weeks in the alive group ($p < 0.001$).

It is worth considering that some studies have found an association between the masculine gender and a risk of death.[2,14,16,23–25,27,28] The studies say that when comparing genders in relation to mortality, it is commonly observed that the death rate of males is higher than that of females at all ages. In our study, when comparing genders, both groups were similar (NS).

The APGAR score has been considered an important predictive variable of neonatal mortality. This variable is more directly related to the quality of attention at delivery, in spite of the influence of previous conditions of the newborn during the intrauterine period, which determines its vitality at birth. This score has been mentioned by various authors[23–25,27,28] as an important variable which is closely related to the risk of death when scores of less than 7 are obtained at the first and fifth minutes. Within our findings, we observed that there were more dead in the low APGAR category ($p < 0.001$).

The important increase of neonatal death rates due to the high prevalence of premature births and low weight at birth has been mentioned in various studies.[27,28] These are closely related to other indicators in the mothers, such as the intake of alcohol, tobacco and illicit drugs. Within our pathological and non-pathological findings on the mothers, we found that the mothers of deceased patients presented a greater relation to alcoholism (<0.05), drug addiction (<0.05) and tattoos (<0.001).

Regarding prematurity, various studies have reported that it is a factor in risks associated with neonatal death, malnutrition, infections, iatrogenic prematurity, hypertension and the premature rupture of membranes, among other things.[17,27–29] In our study, we observed that there were more mothers with arterial hypertension (<0.001) and gestational ($p < 0.05$) diabetes in the dead group. The presence of infections, preeclampsia, eclampsia and other diseases were not significant (NS).

The frequency of prenatal attention is one of the most important things to prevent neonatal death, because when the frequency of prenatal attention is greater, the chance that fetal and maternal illnesses can be detected and early intervention applied is also greater.[23] Regarding prenatal consultations, it has been found that the risk of mortality is 2.32 times greater in the group of mothers which had been to up to 3 consultations, and up to 3.56 times greater in the group of mothers which had not gone to any consultation.[28] Some authors[12,27,28] corroborate these results, finding that the mothers with less than 5 consultations have a 2.5 times higher risk than the others. In the findings of our group, upon comparison of prenatal control, both groups were similar (NS).

de Fátima Almeida et al.,[28] in their study performed at the Federal University of Espíritu Santo in Brazil, studied neonatal deaths as well as the risk factors associated with them, finding a risk of death 3 times higher in mothers that were less than 15 years old (OR = 2.97; IC 95%). This bears a close resemblance to our study, which found that there were more mother that were less than 18 years old in the dead group ($p < 0.01$).

Maternal education is considered an indicator of social status. The mother's level of education can be considered a factor related to her cultural profile and conduct of health care, which has an important effect on the determination of mortality.[23,27,28] This investigation has demonstrated, through an analysis of the correlation between maternal education and obstetrical indicators, that there is a statistically significant association between a low level of education and low weight at birth, an elevated number of premature births and a lesser number of prenatal consultations. Maternal education can be considered to be an obstetrical risk factor for pregnant women and newborns. The analysis also signified that the significant association between neonatal mortality and an inferior education with these women may be due to lower social conditions and limited access health services.[28]

Within the findings of our study, upon comparison of educational levels, we found that there were a greater number of children in the dead group of mothers with a high school education ($p < 0.001$) and there were more children in the alive group of mothers with an elementary school education ($p < 0.001$). Within the findings of our study, we found that, at 72 h, the best sensitivity (95%) was when lactate was lower than 1.5 mmol/l and the best specificity (89%) was with lactate levels higher than 2.5 mmol/l, which is in accordance with medical literature.

Conclusion

According to our findings, we can conclude the following: the study of risk factors in mothers is important in order to prevent premature births as well as its strong connection with low weight at birth and a lower gestational age, since results show that 67% of deaths were under 1500 g and that 61% were under 28 weeks of gestation.

Lactate over 1.5 mmol/l has a sensitivity (to be dead) of 95% at day 3 and 91% at day 7.

When pH is higher than 7.25 there is a specificity (to be alive) of 96% at day 3 and 91% at day 7.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

No financial support was provided.

References

1. García SC, Rupérez L, López-Herce Cid, et al. Valor pronóstico de la puntuación PIM (Índice pediátrico de mortalidad) y del ácido láctico en niños críticamente enfermos. An Esp Pediatr. 2002;57:394–400.
2. Haterill M, McIntyre AG, Wattie M, et al. Early hyperlactataemia in critically ill children. Intensive Care Med. 2000;26:314–8.
3. Singarajah C, Carlson RW. A review of the role of blood lactate measurements in the ICU. J Intensive Care Med. 1998;13:218–28.
4. Henning RJ, Weil MH, Weiner F. Blood lactate as a prognostic indicator of survival in patients with acute myocardial infarction. Circ Shock. 1982;9:307–15.
5. Aduen J, Bernstein W, Khastgir T, et al. The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations. JAMA. 1994;272:1678–85.
6. Sauaia A, Moore F, Moore E, et al. Early predictors of postinjury multiple organ failure. Arch Surg. 1994;129:39–45.
7. Drummond AJ, Bernard GR, Russell JA. Decreasing lactate is associated with lower mortality in patients who have sepsis syndrome. Chest. 1993;104:157.
8. Hatherill M, Sajjanhar T, Tibby SM, et al. Serum lactate as a predictor of mortality after paediatric cardiac surgery. Arch Dis Child. 1997;77:235–8.
9. Shime N, Kaageyama K, Ashida H, et al. Perioperative assessment of blood lactate levels in pediatric heart surgery. Masui. 2001;50:752–7.
10. Deshpande SA, Platt MP. Association between blood lactate and acid–base status and mortality in ventilated babies. Arch Dis Child Fetal Neonatal. 1997;76:F15–20.
11. Caridad SM. Acidosis láctica. Rev Cubana Med. 2000;39:115–9.
12. Mizock BA. Controversies in lactic acidosis implications in critically ill patients. JAMA. 1987;258:497–501.
13. Soliman HM, Vincent JL. Prognostic value of admission serum lactate concentrations in intensive care unit patients. Acta Clin Belg. 2010;65:176–81.
14. Zhou X, Xu ZY, Fan JH, et al. Relationship between blood lactate level and disease severity in critically ill children. Zhongguo Dang Dai Er Ke Za Zhi. 2012;14:114–6.
15. Nadeem M, Clarke A, Dempsey EM. Day 1 serum lactate values in preterm infants less than 32 weeks gestation. Eur J Pediatr. 2010;169:667–70.
16. Basaran M, Sever K, Kafali E, et al. Serum lactate level has prognostic significance after pediatric cardiac surgery. J Cardiothorac Vasc Anesth. 2006;20:43–7.
17. Koliski A, Cat I, Giraldi DJ, et al. Lactato sérico como marcador prognóstico em crianças gravemente doentes. J Pediatr (Rio J). 2005;81:287–92.
18. Murtuza B, Wall D, Reinhardt Z, et al. The importance of blood lactate clearance as a predictor of early mortality following the modified Norwood procedure. Eur J Cardiothorac Surg. 2011;40:1207–14.
19. Borchers A, Wilkins PA, Marsh PM, et al. Association of admission L-lactate concentration in hospitalised equine neonates with presenting complaint, periparturient events, clinical diagnosis and outcome: a prospective multicentre study. Equine Vet J. 2012;44:57–63.
20. Morales SHN, Garza AAG, Rodríguez VI, et al. Índices de riesgo de mortalidad (PRISM y PIM) en niños con respecto a la concentración de lactato a su ingreso a una Unidad de Cuidados Intensivos. Rev Mex Pediatr. 2010;77:111–4.
21. Kirschenbaum LA, Asitiz ME, Rackow HC. Interpretation of blood lactate concentrations in patients with sepsis. Lancet. 1998;352:921–2.
22. Abramson D, Scalca TM, Jitchcock R, et al. Lactate clearance and survival following injury. J Trauma. 1993;35:584–8.

23. Straney LD, Lim SS, Murray CJ. Disentangling the effects of risk factors and clinical care on subnational variation in early neonatal mortality in the United States. PLoS ONE. 2012;7:e49399, http://dx.doi.org/10.1371/journalpone.004939.
24. Tomashek KM, Shapiro-Mendoza CK, Davidoff MJ, et al. Differences in mortality between late-preterm and term singleton infants in the United States. J Pediatr. 2007;151:450–6.
25. Kramer MS, Demissie K, Yang H, et al. The contribution of mild and moderate preterm birth to infant mortality. JAMA. 2000;284:843–9.
26. Rodríguez-Bonito R, Gonzalez-Garcia M. Clasificación del recién nacido. In: Rodríguez BR, editor. Manual de neonatología. 2n ed. México: Mc Graw-Hill Interamericana; 2012. p. 4–12.
27. Mehaffey K, Higginson A, Cowan J, et al. Maternal smoking at first prenatal visit as a marker of risk for adverse pregnancy outcomes in the Qikiqtaaluk (Baffin) Region. Rural Remote Health. 2010;10:1484.
28. de Fátima Almeida LE, Inês SA, Harter GR, et al. Risk factors for neonatal mortality in the city of Serra, Espírito Santo. Rev Bras Enferm, Brasília. 2012;65:578–85.
29. Zhang Y-P, Liu XH, Gao SH, et al. Risk factors for preterm birth in five maternal and child health hospitals in Beijing. PLoS ONE. 2012;7:e52780, http://dx.doi.org/10.1371/journal.pone.0052780.