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Cesarean deliveries and other risks for persistent pulmonary hypertension of the newborn

Parto cesáreo e outros riscos para hipertensão pulmonar persistente do recém-nascido

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ABSTRACT

Objectives: To evaluate risks for persistent pulmonary hypertension in the newborn, confirmed by echocardiography, associated with cesarean deliveries and other factors.

Methods: Cohort of all deliveries >36 weeks within a period of 23 months. A nested case-control study was performed in a subset of the cohort, involving newborns admitted into neonatal intensive care unit with diagnosis of persistent pulmonary hypertension matched with normal controls, with application of questionnaires to mothers to identify risks. Logistic regression was used to calculate odds ratios.

Results: From 9452 newborns, 8388 (88.7%) were delivered by cesarean and 1064 (11.3%) by vaginal delivery. Questionnaires were applied to 173 mothers. Infants from cesareans had a fivefold increased risk of persistent pulmonary hypertension of the newborn: 42 (0.5%) versus 1 case (0.09%) in the vaginal group (OR 5.32, p=0.027). No interactions were found between smoking, parity, arterial hypertension and labor before cesarean section and persistent pulmonary hypertension of the newborn. First minute Apgar score ≤7 and maternal diabetes were related to increased risk.

Conclusion: Reducing cesarean deliveries could prevent many cases of serious persistent pulmonary hypertension of the newborn.

Keywords: Hypertension, pulmonary; Infant, newborn; Cesarean section; Risk factors

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a state of hypoxemia and cyanosis, caused by failure in normal respiratory transition. Pulmonary arterial resistance fails to fall and there is a persistence of right to left shunt across the foramen ovale and arterial duct, with no cardiac primary disease.[1] The incidence of PPHN is reported as 1-2 per 1000 live births, but cesarean deliveries can elevate this incidence up to 1 per 270.[2] PPHN is associated with significant morbidity and mortality, and is not limited to term or post-term neonates with meconium aspiration or sepsis.[3] Cesarean births have been rising around the world. Up to 50% of this procedure may be performed because of prior cesarean delivery, and maternal choice is also a current raising factor.[4] We observed a high number of admissions in the neonatal intensive care unit (NICU), and hypothesized that this fact would be related to the high rates of cesarean deliveries. This study was designed to confirm this hypothesis.

METHODS

Study population

The study was conducted within a tertiary hospital from São Paulo, Brazil, after approval of Institutional Ethics Committee. From November 9, 2005 to October 9, 2007, all deliveries were recorded, with respect to mode of delivery and gestational age. Within this cohort, a nested case-control study[5] was performed: newborns with gestational age ≥ 36 weeks with diagnosis of persistent pulmonary hypertension, admitted into neonatal intensive care unit, were eligible to enter the disease group. Inclusion criteria were serious PPHN, defined by hypoxemia with need for supplemental oxygen for more than 2 days, or any period of invasive and non-invasive mechanical ventilation, to maintain arterial oxygen saturation between 89-95%. Ecocardiography was obligatory to confirm PPHN, documenting right-to-left shunting at foramen ovale, ductus arteriosus or both, without congenital heart disease, and a doppler estimation of pulmonary artery systolic pressure >35 mmHg or mean pulmonary artery pressure >20 mmHg. [6]

Exclusion criteria were evidence of meconium aspiration, pneumonia, sepsis, diaphragmatic hernia, intra-uterine growth restriction and gestational age <36 weeks. Mothers of babies with PPHN were invited to respond to a questionnaire, containing information on smoking, labor (defined as regular uterine contractions and cervical dilation >1 cm), parity, maternal age, diabetes, systemic hypertension, prior abortions, anesthesia and analgesia. For each newborn from disease group, 3 non-symptomatic normal newborns were included as controls. The same questionnaire was applied to mothers of controls. All the mothers in case-control study signed an informed consent form, and their infants were followed prospectively from birth to discharge.

Data processing and statistical analysis

Questionnaire forms were revised and entered on to a Microsoft Access database. Statistical analyses were performed using SPSS version 10.0.1 (SPSS Inc, USA). With cohort data, a logistic regression model with cesarean section as a predictor of PPHN was used to determine odds ratio. Overall model fit chi-square was obtained to validate model. Odds were also calculated to assess the interaction between the variables obtained from questionnaires and symptomatic cases and controls. For comparing means we used independent samples T test.

RESULTS

Among 10075 live born infants, 623 were excluded from analysis due to exclusion criteria, leaving 9452. From these, 8388 (88.7%) were delivered by cesarean section, and 1064 (11.3%) by vaginal delivery. Compared to those delivered by vaginal delivery, the infants with gestational age >36 weeks delivered by cesarean section had a fivefold increased risk of persistent pulmonary hypertension: there were 42 cases (0.5%) in

Table 1 - Interactions of control and symptomatic groups

Variables	PPHN group (n = 43)	Controls (n = 130)	OR (95% CI)	P value
Weight (g)	3185 ± 495 (2400 - 4810)	3191 ± 362 (2600 - 4410)	-	0.1
Gestational age (weeks)	37.70 ± 1.14 (36 - 40)	38.89 ± 0.98 (36 - 41.14)	-	< 0.001
Male gender	30 (69.7)	67 (51.5)	2.17 (1.03 - 4.53)	0.03
Active or passive smoking, all length of pregnancy	15 (34.8)	34 (26.1)	1.54 (0.70 - 3.34)	0.28
Active smoking, all length of pregnancy, >10 cigarettes/day	3 (6.9)	16 (12.3)	0.62 (0.16 - 2.27)	0.47
Parity	2.22 ± 1.28 (1 - 7)	1.77 ± 0.94 (1 - 5)	-	0.10
Maternal age (years)	25.65 ± 11.9 (21-39)	28.26 ± 5.7 (19-41)	-	0.12
Apgar ≤7 at 1st minute	16 (37.2)	26 (20.0)	2.37 (1.11 - 5.03)	0.027
Apgar ≤7 at 5th minute	3 (2.3)	0 (0.0)	-	0.57
At least 1 prior abortion	13 (10.0)	6 (13.9)	1.5 (0.53 – 4.23)	0.40
Maternal arterial hypertension	6 (13.9)	20 (15.4)	0.89 (0.33 - 2.38)	0.81
Maternal diabetes (type 1 or gestational)	5 (11.6)	2 (1.5)	8.42 (1.57 – 45.15)	0.008

PPHN - persistent pulmonary hypertension of the newborn; OR – odds ratio; CI - confidence interval. Results are expressed in mean±standard deviation (range) or number(%)

cesarean group, versus only 1 case (0.09%) in the vaginal delivery group (OR 5.32, p = 0.027 by chi-square for overall model fit). Questionnaires were applied to a total of 173 mothers in the nested case-control study (n = 43 in the disease group, 130 in control group), and medical charts of all these mothers were reviewed. In the control group, there were 106 cesareans and 24 vaginal deliveries. From the total of 148 cesarean deliveries (42 with disease + 106 in control group), 20 (13.5%) were done because of obstetric emergencies like breech presentation, fetal distress with meconium-stained amniotic fluid and maternal eclampsia or preeclampsia. Seventy three (49.3%) were done because of prior cesareans, and 55 (37.2%) were planned as a choice by the mothers, without no apparent clinical impediment to vaginal delivery. Table 1 depicts data and statistical analysis from the case-control study. We did not find interactions between active smoking of any quantity of cigarettes/day (<10; between 10 and 20; >20) or between passive smoking, in part or totality of pregnancy, and PPHN. No interactions were found also between PPHN and number of prior pregnancies or abortions, age of mothers, maternal arterial hypertension and labor before cesarean section. First minute Apgar score < or equal to 7 and maternal diabetes were related to increased risk for PPHN.

Neonates with PPHN stayed in NICU for a mean of 16 days (3 - 66). Twenty-six (60.4%) needed invasive mechanical ventilation for a mean of 4.8 days (0.4 - 9), and 19 (44.1%) received nitric oxide for a mean of 3.6 days (2 - 7). Vasoactive drugs were required in 25 (58.1%) for a mean of 4.4 days (2 - 10). One infant died at age of two months, after discharge and readmission, from pulmonary sequelae and pneumonia.

DISCUSSION

Elective cesareans have been reported to carry at least a fivefold higher risk for PPHN when compared to vaginal deliveries.[2,3] In 1977, Csaba et al. suggested that, since prostaglandins are intimately involved in pulmonary adaptation after delivery, the observed decreased prostaglandin production after elective cesarean would be one of the factors responsible for increased pulmonary vascular resistance of the newborn with PPHN.[7] As uterine activity is associated with high prostaglandin production, it could be expected that labor before cesarean would protect against PPH, but the risk is similarly high for cesarean with and without preceding labor, as we and others[3] observed. Fetal compression in the birth canal can expels liquid from lungs and airway, and this can be a beneficial effect of vaginal delivery which is lacking in cesareans.[8] Jaillard et al. reported that levels of norepinephrine similar to those observed at birth induce a potent pulmonary vasodilation in lungs of fetal lambs, involving α_2-adrenoceptors activation and nitric oxide production. Lower levels of norepinephrine are observed in newborns from cesarean deliveries.[9]

Inflammatory activity is different in neonates delivered by cesarean section or exposed to labor,[10] and an increased thromboxane-prostacyclin ratio is characteristic in PPHN.[11] We speculate that inflammation can play a major and still unexplored role in PPHN genesis.

In the city of São Paulo, in the year of 2005, cesareans counted for 53.2% of all deliveries. These rates are maintained by vaginal deliveries in public health services, since rates of cesareans higher than 90% can be observed in private hospitals.[12] This dissociation can be explained by the number of cesareans performed in private hospitals by patient's choice or request, that we reported being near to 40%. This new tendency, together with the near 50% of mothers with prior cesareans, can help to understand the abnormally high number of serious cases of PPHN we observed in our NICU. The observed lower gestational age of newborns with PPHN suggests that this morbidity would be lower if elective or requested cesarean could be postponed to 39 or 40 weeks gestation.[3,13]

We also observed a higher number of diabetic mothers in PPHN group. Diabetes has been associated with PPHN: insulin resistance can induce endothelial dysfunction and inflammation[14] with possible repercussion on development of fetal lung, but Hernández-Diaz et al. reported that the odds ratio for diabetes became null when mode of delivery was included in regression model, speculating that diabetes increases risk for PPHN increasing the number of cesarean deliveries.[3] As our few cases of diabetes all resulted in cesareans, we were not able to perform this kind of analysis. The relationship between Apgar <7 at 1st minute and PPHN can be explained by the fact that hypoxia can cause pulmonary vasoconstriction.[11] There was a modest increased risk for boys, a well known but unexplained association.

A limitation of this study is the nested case-control design, suitable to study main effects but possibly inadequate for effect modification. Cologne et al. report that 5-6 controls per case would be needed in this kind of study to achieve 90% of the maximum cohort level of statistic power.[15] The strength of the study is the large cohort for the main effect and the strict definition for PPHN.

CONCLUSION

Cesarean section, maternal diabetes and 1st minute Apgar <7 were associated with higher risk for PPHN. The high percentage of mothers that demand cesareans as a choice and mothers with prior cesareans can explain the elevated incidence of serious PPHN we observed. Reducing cesarean deliveries could prevent many cases of serious HPPN.

RESUMO

Objetivos: Avaliar os riscos para hipertensão pulmonar persistente do recém-nascido, confirmada por ecocardiografia, associada a partos cesáreos e outros fatores.

Métodos: Coorte de todos os nascimentos com idade gestacional acima de 36 semanas em um período de 23 meses. Um estudo caso-controle aninhado foi feito em uma parte da coorte, envolvendo um grupo de recém-nascidos com diagnóstico de hipertensão pulmonar persistente do recém-nascido comparados com um grupo de controles normais, com aplicação de questionários às mães para identificação de riscos. Regressão logística foi utilizada para calcular *odds ratios*.

Resultados: De 9452 recém-nascidos, 8388 (88,7%) nasceram de cesáreas, e 1064 (11,3%) de parto vaginal. Questionários foram aplicados a 173 mães. Recém-nascidos de cesáreas apresentaram um risco 5 vezes maior de hipertensão pulmonar persistente do recém-nascido: 42 casos (0,5%) versus 1 caso (0,09%) entre os de partos vaginais (OR 5,32, p=0,027). Não foram observadas interações entre tabagismo, paridade, hipertensão arterial materna e trabalho de parto antes da cesárea e a hipertensão pulmonar persistente do recém-nascido. Apgar no 1º minuto ≤7 e diabetes materno se relacionaram a um risco aumentado.

Conclusão: A redução do número de partos cesáreos poderia prevenir muitos casos graves de hipertensão pulmonar persistente do recém-nascido.

Descritores: Hipertensão pulmonar; Recém-nascido; Cesárea; Fatores de risco

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