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ORIGINAL ARTICLE

Mode of delivery and antenatal steroids and their association with survival and severe intraventricular hemorrhage in very low birth weight infants

ME Hübner, R Ramirez, J Burgos, A Dominguez, JL Tapia and the Neocosur Neonatal Network[1]

OBJECTIVE: To determine whether CS delivery and receipt of antenatal steroids (ANS) in vertex-presenting singletons with a gestational age (GA) between 24 and 30 weeks is associated with improved survival and improved severe intraventricular hemorrhage (sIVH)-free survival.

STUDY DESIGN: Multicenter cohort, retrospective analysis of prospectively collected data. Vertex-presenting singletons newborns with GA 24 to 30 weeks, birth weight between 500 and 1500 g, without major congenital malformations, born between 2001 and 2011 at Neocosur centers were included.

RESULTS: Four thousand three hundred and eighty-six infants fulfilled inclusion criteria: 45.8% were delivered vaginally and 54.2% by cesarean section (CS). Newborns delivered vaginally received less ANS, had lower GA, Apgar scores and a lower incidence of survival and sIVH-free survival ($P < 0.001$). Newborns with better survival were those with ANS, independent of mode of delivery. At 24 to 25 weeks GA, increased survival and sIVH-free survival were associated with ANS and CS delivery, compared with those who received ANS and delivered vaginally.

CONCLUSIONS: Among vertex-presenting singletons with GA 24 to 30 weeks, better survival and IVH-free survival were associated with ANS, independent of mode of delivery. In infants at 24 to 25 weeks gestation the combination of ANS/CS was associated with improvement in both outcomes.

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INTRODUCTION

There has been considerable improvement in the survival rate of very low birth weight (VLBW) infants over the past decades. Numerous strategies have been demonstrated to have impact on the morbidity and mortality of VLBW infants, the most fundamental of which are the organization and regionalization of perinatal care, the place of birth and the availability of neonatal intensive care.[1,2]

In the ongoing search to improve outcomes, the issue of the best mode of delivery for VLBW newborns has not been resolved. The Term Breech Trial[3] recommended cesarean section (CS) for breech presentation, which has higher risk of asphyxia, cord prolapse and head entrapment; the recommendation for CS delivery has been extended to VLBW newborns without rigorous randomized controlled trials.[4] More recently, CS delivery has been considered to improve survival in growth-restricted VLBW infants, regardless of presentation.[4] However, it remains unclear whether CS in combination with antenatal steroids (ANS) results in decreasing mortality and morbidity, for example, intraventricular hemorrhage (IVH), in vertex-presenting VLBW infants.[5–7] Administration of ANS to a woman in labor with a preterm fetus is a proven, effective therapy to mature the 24 to 34 weeks gestational age (GA) fetus, reducing death, respiratory distress syndrome and intracranial hemorrhage.[8–10] Therefore, whether the combination of ANS treatment and CS delivery of a woman in active labor with a vertex-presenting VLBW fetus would be associated with better short-term outcomes is an important clinical question.

The primary objective of this study is to determine whether ANS treatment and CS delivery in vertex-presenting singletons with a GA between 24 and 30 weeks is associated with improved survival and improved severe IVH (sIVH)-free survival.

We hypothesized that VLBW infants delivered by CS after receiving ANS would have a higher chance of survival and sIVH-free survival than those delivered vaginally without ANS.

MATERIAL AND METHODS

Study population

The Neocosur Network is a cooperative, nonprofit association established in 1997 to support research on the safety and efficacy of treatments to improve neonatal health in the region (www.neocosur.org). It includes 25 tertiary neonatal centers in Argentina, Brazil, Chile, Paraguay, Peru and Uruguay. Neocosur prospectively records data on all liveborn VLBW neonates whose birthweight ranges from 500 to 1500 g, born in the participating centers, using predefined diagnostic criteria and an online registry system. GA is determined by the best obstetrical estimate, usually including an ultrasound before 12 weeks of pregnancy. Data for this study were obtained from the Network database during 2001 to 2011. The sample included all singleton, liveborn 500 to 1500 g, 24 to 30 weeks gestation vertex-presenting fetuses who were free from major congenital anomalies born in the participating centers.

Neonatology, Santiago, Chile. Correspondence: Professor ME Hübner, Hospital Clínico Universidad de Chile and Clínica Alemana de Stgo. - U. del Desarrollo, Neonatology, Los Monjes 12172, Las Condes, Santiago 7610548, Chile.
E-mail: mehubner@gmail.com
[1]The collaborators from the Neocosur Network Collaborative Group are listed before References.
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Variables analyzed

The following demographic and perinatal variables were used to describe the newborns: birth weight (BW), GA 24 to 30 weeks, gender, small for gestational age (SGA),[11] 1- and 5-min Apgar scores, mode of delivery (CS or vaginal), receipt of ANS (mothers who had received at least one dose of ANS), premature (before onset of labor) prolonged (>18 h) rupture of membranes in preterm pregnancies (PPROM), early-onset sepsis (defined as clinical findings confirmed with a positive blood or cerebrospinal fluid culture by 72 h after birth), sIVH (IVH grades III and IV[12]), and death before discharge (including death in the delivery room).

Newborns were classified into four groups by combinations of mode of delivery and ANS administration: exposed to ANS treatment and delivered by CS, exposed to ANS treatment and vaginal delivery, not exposed to ANS treatment and delivered by CS, and not exposed to ANS treatment and vaginal delivery. Outcome variables were survival (discharged alive) and sIVH-free survival (neither death nor sIVH).

Statistical analysis

Neonatal demographic and perinatal characteristics were described using mean and s.d. or percentage of cases according to mode of delivery. Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables were used to calculate *P*-values.

Prespecified analysis consisted of the comparison of the two outcomes, survival and sIVH-free survival, among the four combined categories of mode of delivery and ANS administration; the group of infants delivered by CS with ANS was set as the reference category for optimal therapy. Logistic regression was used to estimate unadjusted and multivariate odds ratios (OR) and 95% confidence intervals (95% CIs). Covariates included in multivariate regression were gender, PPROM >18 h, Apgars <3 at 1 and 5 min, SGA and early-onset sepsis.

We were interested in analyzing the most vulnerable to intact survival infants, that is, those with GA 24 to 25 weeks, as well as those with GA 26 to 30 weeks.

All data available from the Neocosur Neonatal network was eligible before excluding criteria. Therefore, a power analysis was performed. For survival, all contrasts had a power of at least 95%, except for the comparison between vaginal delivery with use of ANS and CS delivery with use of ANS, which had a power of 78%. For IVH-free survival, all contrasts had a power of at least 95%.

Significance was set at $P<0.05$. Statistical analyses were performed using the SPSS 17.0 software (Chicago, IL, USA).

Ethics Committee

This study was approved by the local Ethics Committee at Schools of Medicine from Universidad de Chile and Pontificia Universidad Católica de Chile.

RESULTS

A total of 4386 newborns met inclusion criteria; 45.8% were delivered vaginally and 54.2% by CS. Overall survival ranged from 28.6% at 24 weeks GA to 84.7% at 30 weeks GA, whereas sIVH-free survival ranged from 20.5% in newborns 24 weeks GA to 83.5% at 30 weeks GA (data not shown). Figure 1 plots the percentage of survival (Figure 1a) and sIVH-free survival (Figure 1b) by GA for four combinations of mode of delivery and ANS treatment. Both survival and sIVH-free survival increase with GA.

Table 1 compares the anthropometric and perinatal characteristics of the study population by mode of delivery. Mean GA and BW and the percentage of ANS receipt and 1- and 5-min Apgar's score $\leqslant 3$ were lower among vaginally delivered newborns compared with those born by CS. Among newborns delivered by CS, a smaller percent were 24 to 25 weeks, had PPROM and early-onset sepsis than among newborns delivered vaginally. The percent surviving and surviving without sIVH was higher among newborns delivered by CS than among newborns delivered vaginally.

Unadjusted regression analysis suggested that receipt of ANS and CS delivery were associated with the highest levels of survival and sIVH-free survival among the four combinations of ANS receipt and delivery mode. The unadjusted OR for neonates who received ANS but delivered vaginally was associated with a decreased OR for survival and those who did not receive ANS, whether delivered by CS or vaginally, had decreasing unadjusted odds for survival and sIVH-free survival when compared with infants delivered by CS with ANS (Table 2, Regression Model 1). Similar results were obtained for 24-to-25-week GA neonates in Regression Model 2, in which gender, Apgar scores, early-onset sepsis, SGA and PPROM were added to the model with the same four combinations of ANS and CS delivery. In the GA 24 to 25

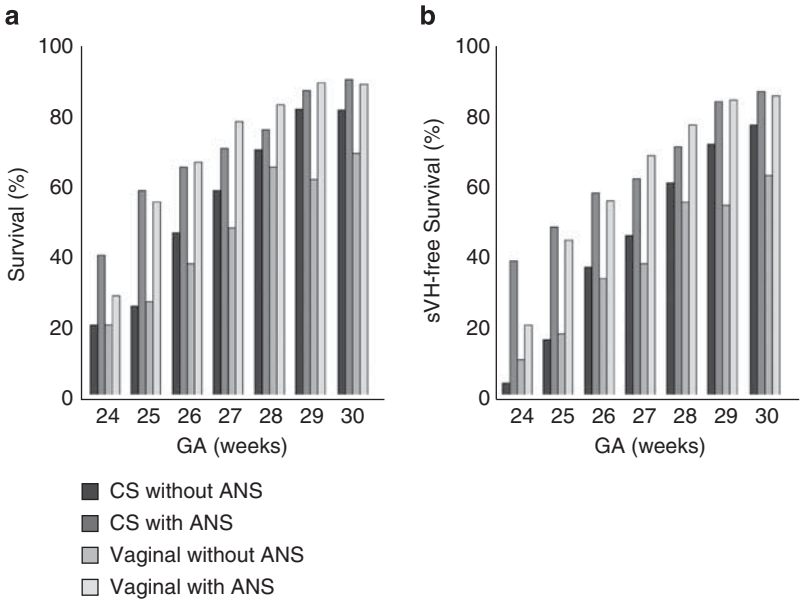

Figure 1. Survival and severe intraventricular hemorrhage (sIVH)-free survival by mode of delivery and antenatal steroids (ANS) by gestational age (GA), Neocosur Network, 2001 to 2011. Both survival (**a**) and sIVH-free survival (**b**) increase with GA. The group of newborns whose mothers did not receive ANS and were born by vaginal delivery had the lowest survival rate. Survival progressively increased in the group of newborns whose mother did receive ANS and were born vaginally, the group of newborns with cesarean section (CS) delivery whose mothers did not receive ANS and the group of newborns with CS delivery whose mothers did receive ANS.

group, all combinations of ANS treatment and mode of delivery were associated with a lower adjusted OR of survival and sIVH-free survival compared with those receiving the combination of ANS treatment and CS delivery.

However, the results of Model 3, among the 26-to-30-week GA newborns, differed from those of Models 1 and 2. In the 26-to-30-week GA neonates, survival was similar among those who had received ANS, independent of delivery mode. Compared with those who had received ANS and were delivered by CS, only the group of infants who did not receive ANS and were born vaginally showed a lower OR for survival (OR 0.35; 95% CI = 0.28 to 0.46). Similarly, among 26-to-30-week GA neonates, survival without sIVH was similar among those who had been exposed to ANS, whether they were delivered by CS or vaginally; in contrast, those who were not exposed to ANS were at lower chances of sIVH-free survival, whether delivered by CS (OR 0.72; 95% CI = 0.54 to 0.96) or delivered vaginally (OR 0.36; 95% CI = 0.28 to 0.46).

Table 1. Anthropometric and perinatal characteristics by mode of delivery, Neocosur Network, 2001–2011

Characteristic	*Vaginal*	*Cesarean*	*Total*	P-*value*
	n = *2009*	n = *2377*	n = *4386*	
GA ⩽ 25 weeks (%)	21.6	9.7	15.1	< 0.001
Weight, g (mean ± s.d.)	1038 ± 265	1018 ± 249	1027 ± 256	0.013
Male (%)	53.7	50.9	52.2	0.066
Apgar 1 ⩽ 3 (%)	26.3	20.5	23.2	< 0.001
Apgar 5 ⩽ 3 (%)	7.7	4.7	6.1	< 0.001
Antenatal steroid use (%)	68.9	84.5	77.3	< 0.001
PPROM > 18 h (%)	41.1	24.9	32.3	< 0.001
Early-onset sepsis (%)	4.9	3.3	4.0	0.010
SGA (%)	24.2	42.4	34.1	< 0.001
sIVH (%)	16.9	10.7	13.4	< 0.001
Survival (%)	67.7	77.0	72.7	< 0.001
sIVH-free survival (%)	60.2	71.1	66.1	< 0.001

Abbreviations: GA, gestational age; PPROM, premature prolonged rupture of membranes; SGA, small for gestational age; sIVH, severe intraventricular hemorrhage.

DISCUSSION

Our results suggest that receipt of ANS, independent of the mode of delivery, may be associated with improvement in survival and sIVH-free survival in vertex-presenting 500 to 1500 g, 24-to-30-week singletons. In the more immature infants (24 to 25 weeks GA), the combination of ANS and CS was associated with an improvement in these two important short-term outcomes.

Because CS delivery of mothers with fetuses at the borderline of viability may expose the mother to a higher risk of morbidity and increase the risk of surgical delivery in future pregnancies,[13–16] the birth attendant and the parents must balance risk to the mother with the potential benefit to the fetus.

Our study suggests that neonates delivered vaginally had lower BW and GA and less exposure to ANS, conditions associated with an increased the risk of death or IVH. It is likely that less aggressive obstetric care and management at birth and parental preference, especially in newborns at the limit of viability, contributed to the choice of vaginal delivery without ANS. If a fetus is not considered viable and/or has a poor prognosis for intact survival, it is more likely that it will be delivered vaginally to minimize maternal effects, despite evidence that active intervention including CS and ANS/CS delivery are associated with improved survival in newborns between 22 and 25 weeks GA.[17]

Our results document poorer survival with vaginal delivery in the absence of ANS administration in VLBW neonates, but the registry does not include the complex data required to document medical indications that would preclude full support or parental preferences.

Our results support and re-emphasize the beneficial effects of ANS in mothers at risk of a very preterm delivery. This contrasts with a recent randomized controlled trial in the developing world in which ANS did not demonstrate benefits; on the contrary, it increased mortality in low- and middle-income countries.[18] One possible explanation for this difference is that the participating Global Network centers included places with very limited resources without any neonatal intensive care unit.

We found differences in survival free of sIVH between the two modes of delivery in newborns who received ANS at 24 to 25 weeks GA where the combination of CS and ANS was associated with a better outcome. Deulofeut *et al*.[19] studied newborns with BW < 1251 g in any presentation and found

Table 2. Multivariate logistic regression for survival and sIVH-free survival, Neocosur Network, 2001–2011

	Regression model 1			*Regression model 2*			*Regression model 3*		
	OR	*95% CI*	P-*value*	*OR*	*95% CI*	P-*value*	*OR*	*95% CI*	P-*value*
Survival									
Use of ANS-mode of delivery									
Received ANS and born by CS	1.00			1.00			1.00		
Received ANS and delivered vaginally	**0.82**	**(0.70–0.97)**	**0.018**	**0.62**	**(0.41–0.92)**	**0.019**	1.00	(0.80–1.25)	0.973
No ANS and born by CS	**0.53**	**(0.42–0.68)**	**< 0.001**	**0.33**	**(0.14–0.74)**	**0.007**	0.86	(0.63–1.18)	0.341
No ANS and delivered vaginally	**0.27**	**(0.22–0.33)**	**< 0.001**	**0.30**	**(0.18–0.50)**	**< 0.001**	**0.35**	**(0.28–0.46)**	**< 0.001**
sIVH-free survival									
Use of ANS-mode of delivery									
Received ANS and born by CS	1.00			1.00			1.00		
Received ANS and delivered vaginally	**0.77**	**(0.66–0.89)**	**0.001**	**0.56**	**(0.37–0.85)**	**0.006**	0.91	(0.74–1.11)	0.334
No ANS and born by CS	**0.48**	**(0.38–0.60)**	**< 0.001**	**0.14**	**(0.05–0.42)**	**< 0.001**	**0.72**	**(0.54–0.96)**	**0.023**
No ANS and delivered vaginally	**0.26**	**(0.21–0.32)**	**< 0.001**	**0.22**	**(0.12–0.38)**	**< 0.001**	**0.36**	**(0.28–0.46)**	**< 0.001**

Abbreviations: ANS, antenatal steroid; CI, confidence interval; CS, cesarean section; OR, odds ratio; sIVH, severe intraventricular hemorrhage. Regression Model 1 included four combinations of way of delivery and use of ANS as explicative variable. Regression Model 2 included variable in Model 1 plus gender, 1-min Apgar score ⩽3, 5-min Apgar score ⩽3, early-onset sepsis, premature prolonged rupture of membranes >18 h and small for GA for the subgroup of newborns with GA 24 to 25 weeks. Regression Model 3 included variables in Model 2 for the subgroup of newborns with GA 26 to 30 weeks. Bold emphasizes important results explained in the text.

increased incidence of sIVH in those < 750 g delivered vaginally compared with those delivered by CS.

A previous study in our network found that vaginal delivery and the non-use of ANS were risk factors for sIVH in newborns < 1250 g BW.[20] In contrast, a recent meta-analysis[21] compared planned CS with vaginal deliveries and did not find any significant differences in neonatal prognosis.

The strengths of this study are that it is a multicenter, large sample-sized study and realized in a middle-income or developing countries. Nonetheless, it has several limitations in addition to its observational design. There are differences in practices among centers regarding infants < 24 weeks gestation; however, for those $\geqslant 24$ weeks GA and $\geqslant 500$ g BW all centers provide full care. In order to limit for this treatment bias, this study excluded infants < 24 weeks GA and < 500 g of BW. The average 75% ANS use is low in comparison with study populations that have reached $\geqslant 90\%$. However, this is corrected in the analysis and precisely this study reinforces the importance of ANS administration. Finally, as it includes only infants from 500 to 1500 g, there may be a few infants, although we cannot estimate their percentage, who did not enter this analysis in the studied GA categories.

In summary, in vertex-presenting singletons with BW within 500 to 1500 g, GA 24 to 30 weeks and without malformations, ANS was associated with better survival and IVH-free survival independent of the mode of delivery, although higher in the combined ANS/CS group. In infants 24 to 25 weeks gestation, the combination of ANS with CS was associated with improved both outcomes, as compared with vaginal delivery, either with or without ANS.

Further research including large studies and in different settings about the best mode of delivery for the more immature and vulnerable newborn infants seem necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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COLLABORATORS FROM THE NEOCOSUR NETWORK COLLABORATIVE GROUP

The following collaborators from the Neocosur Network collaborative group participated in this study: Argentina: Guillermo Colantonio, Jorge Zapata, Gaston Perez, Susana Garcia Ana Pedraza (Clinica y Maternidad Suizo Argentina, Buenos Aires); Isabel Kurlat, Oscar Di Siervi, Adriana Escarate (Hospital de Clinicas Jose de San Martin); Gonzalo Mariani, Jose Maria Ceriani, Silvia Fernandez, Carlos Fustinana, Pablo Brener, Eleonora Edwards (Hospital Italiano, Buenos Aires); Jorge Tavosnaska, Liliana Roldan, Hector Sexer, Gladys Saa, Debora Sabatelli, Maria Laura Gendra, Maria Fernanda Buraschi, Paula Molina (Hospital Juan Fernandez, Buenos Aires); Daniel Agost, Federico Morganti, Adriana Fontana, Daniela Chandias, Monica Rinaldi (Hospital Lagomaggiore, Mendoza); Carlos Grandi, Elio Rojas, Claudio Solana, Ricardo Nieto, Javier Meritano, Miguel Larguia, Laura Kasten, Lucrecia Cuneo (Maternidad Sarda, Buenos Aires); Marcelo Decaro, Lionel Cracco, Gustavo Bassi, Noemi Jacobi, Andrea Brum, Nestor Vain (Sanatorio de la Trinidad, Buenos Aires); Adriana Aguilar, Miriam Guerrero, Edgardo Szyld, Alcira Escandar (Hospital Dr Diego Paroissien, Buenos Aires); Daniel Abdala, MartinGuida, Lucila Ferrin, Horacio Roge (Hospital Español de Mendoza); Gabriel Musante, Maria C. Capelli, Juan Pablo Berazategui, Magdalena de Elizalde, Juan Ignacio Fraga, Rodolfo Keller (Hospital Universitario Austral, Buenos Aires); Luis Ahumada, Mirta Ferreyra (Hospital Nuestra Señora de la Misericordia, Cordoba); Brazil: Vanda Ferreira, Roberta Borges, Marynea Do Vale, Silvia Cavalcante, Joama Gusmao, Patricia Franco, Maria Jose Silva (Hospital Universidad Federal de Maranhao, Sao Luis); Chile: Jorge Fabres, Alberto Estay, Alvaro Gonzalez, Javier Kattan, Mariela Quezada, Soledad Urzua (Hospital Clinico Pontificia Universidad Catolica de Chile, Santiago); Lilia Campos, Lilian Cifuentes, Jorge Leon, Roxana Aguilar, Sergio Treuer, Jimena Giaconi, Aldo Bancalari (Hospital Guillermo Grant, Concepcion); Jane Standen, Marisol Escobar, Viviana Veas, Daniela Sandino (Hospital Gustavo Fricke, Viña del Mar); Agustina Gonzalez, Claudia Avila, Carla Guzman (Hospital San Jose, Santiago); Claudia Toro, Patricia Mena, Beatriz Milet, Enrica Pittaluga (Hospital Dr Sotero del Rio, Santiago); Veronica Peña, Rafael Mendizabal, Dagoberto Pizarro (Hospital San Borja Arriaran, Santiago); Ivonne D'Apremont, Jose L Tapia, Guillermo Marshall, Luis Villarroel, Mariela Quezada, Angelica Dominguez (Unidad Base de Datos, Pontificia Universidad Catolica de Chile, Santiago). Paraguay: Jose Lacarruba, Elizabeth Cespedes, Ramon Mir, Elvira Mendieta, Larissa Genes, Carlos Caballero (Departamento de Hospital de Clinicas de Asuncion). Peru: Veronica Webb, Fabiola Rivera, Margarita Llontop, Sicilia Bellomo, Jaime Zegarra (Hospital Cayetano Heredia, Lima); Oscar Chumbes, Anne Castañeda, Walter Cabrera, Raul Llanos, Jorge Mucha, Gustavo Garcia (Hospital Guillermo Almenara, Lima). Uruguay: Beatriz Ceruti, Daniel Borbonet, Sandra Gugliucci, Ana Lain, Mariza Martinez, Gabriela Bazan, Susana Piffaretti, Isabel Cuña, Patricia Bermudez (Facultad de Medicina Servicio de Recien Nacidos).

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