 doi:10.20944/preprints202112.0258.v2

Title: Neonatal Intra-Ventricular-Hemorrhage prevention in premature at < 30 weeks gestational Age, a 12 years' experience

Authors
Angela B. Hoyos 1,2, a, Pablo Vasquez-Hoyos 3,4,5, b.
Affiliations
1. MD. Division of Neonatology, Clinica del Country, Bogota, DC, Colombia.
2. Professor of Pediatrics, Universidad El Bosque, Bogota, Colombia.
3. MD, MSc. Sociedad de Cirugía Hospital de San José, Bogota, Colombia.
4. Department of Pediatrics. Universidad Nacional de Colombia, Bogota, Colombia.
5. Department of Pediatrics. Fundación Universitaria de Ciencias de la Salud, Bogota, Colombia.
ORCID:
a. https://orcid.org/0000-0002-5403-3268
b. https://orcid.org/0000-0002-4892-5032

Corresponding autor: Dr. Angela Hoyos; Unidad de Neonatología, Clínica del Country, Cra 16 # 82-57, Bogotá, Colombia. Cel: +57 3157926533. Email: angela.hoyos@clinicadelcountry.com.

Abstract

Introduction: Intraventricular Hemorrhage (IVH) is a devastating condition mostly in preterm infants at < 30 weeks GA with large morbidities and mortality usually in the first 72 hours after birth. Prevention seems to be the only way to completely deal with this problem. The IVH prevention in this age group has been studied and includes some strategies such as prenatal corticosteroids, cesarean delivery, careful extraction among others, but still, it has an unacceptably high incidence in this population. A protocol with the name Drive to Zero IVH Prevention Project that was presented in one of EpicLatino conferences some years ago. As with any quality improvement in practices, we adapted this project to our unit.

Objective: To compare the IVH incidence in our unit after the protocol implementation with and historic cohort from the same unit and with all other units un the epilactino network.

Material and method: In October 2017 we begun to implement a neuro protection protocol. For this analysis we include every patient born <30 weeks of GA, inborn or outborn but less than 2 days old, that

 doi:10.20944/preprints202112.0258.v2

survived at least three days and had a neuroimaging preformed. We include cases until July 2022, and we use the EpicLatino, a Latin-American database, from 2018 to 2020 excluding our own unit for comparison as well as an historical cohort from our unit from 2010-2017. The protocol consists of: Minimal manipulation, low volume ventilation, one routine fiscal exam a day, neutral head position, one blood pressure measured per shift, no keel stick measurements, continuous dim light and low noise level, minimal touch, no vasoactive therapy except in extreme cases, temperature and humidity at 80%, catheters, when possible, fluid restriction followed with diuresis, no PDA therapy or Echo if possible and routine therapy with hydrocortisone, erythropoietin, caffeine, parenteral nutrition, and trophic feeding. e performed a univariate analysis for IVH and groups and a logistic regression model with variables that had statistical significance in the univariate analysis.

Results: The study group included 64 cases, the historic cohort 123 and the EpicLatino 1029. Demographic characteristics were similar with few statistically significant differences. We found four grade 1-2 and six grade 3-4 IVH in the study group (some caused by very traumatic delivery with multiples hematomas in head, body, and extremities), all significantly lower that the other two groups. The logistic regression model confirmed the independent statistically significant result in the study group.

Conclusion: The hemorrhage during delivery must be prevented by the obstetric team. Afterwards, a set of interventions like very gentlehandling with minimal manipulation and unnecessary strict lab managing seams to decrease the incidence of IVH.

 doi:10.20944/preprints202112.0258.v2

Main Text

Introduction

Intra-Ventricular-Hemorrhage (IVH) is a devastating condition mostly in preterm infants < 30 weeks gestational age (GA) at birth, with large morbidities and mortality.[1-3] The timing of the IVH has been studied and seems to occur early (first 6 hours of life)[4,5] but it may continue developing, and most cases can be found in the first 72 hours after birth.[6] Probably, hemorrhage at delivery due to obstetric complications accounts for many cases. Observational data has demonstrated that elective cesarean section has been associated with a reduced risk of IVH in preterm infants <30 weeks GA when presenting with preterm labor.[7] Identified risk factors as Germinal matrix immaturity and fluctuations in the cerebral blood flow have been described as risk-factors for IVH.[8,9] In clinical settings, low birth gestation and weight, lack of antenatal corticosteroids, Apgar score <5 at 5 min, respiratory distress syndrome, early onset sepsis, hypercapnia, pCO_2 fluctuations, inotropes or normal saline boluses, metabolic disorders, opioids infusions, and bicarbonate/THAM therapy have been implicated.[6,7,10]

Prevention seems to be the only way to completely deal with this problem. The IVH prevention in this age group hasbeen studied and includes some strategies such as prenatal corticosteroids,[11] cesarean delivery,[7] careful extraction among others and nurse practices,[12] but still it has an unacceptably high incidence in this population.

Epiclatino is a database of neonatal intensive care units in Latin America, based on the CNN (Canadian Neonatal Network) collection instrument and quality improvement programs.[13] Clinica del Country is a third level hospital located in Bogota, Colombia with high-risk deliveries and with a third level neonatal unit.

Objective

To compare the IVH incidence in our unit after the protocol implementation with and historic cohort from the same unit and with all other units un the epilactino network

Material and method

In October 2017, a protocol was presented and approved at the Clínica del Country unit as a strategy to adapt the changes of minimal manipulation to the already existing prevention strategies. This strategy consists of the following:

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202112.0258.v2

New Handling

Minimal manipulation as follows:

- Ventilatory parameters as needed and volume ventilation when possible.
- Only one routine fiscal exam a day. No routine measurements or weight
- Maintain neutral head position[15] and bed elevated 30 degrees.
- Only 1 blood pressure a shift.
- No keel stick measurements (glucose measurement once a day with blood gases)
- Continuous dim light less than 20 Lux when possible and noise level less than 45 dB
- Minimal touching except to clean perinatal area and change dippers when needed
- No hypotension therapy except in extreme cases

Old Handling

- Temperature and humidity 80%
- Catheters when possible
- No PDA therapy or Echo if possible
- Routine therapy:
    - Hydrocortisone 0.5 mg/kg/day in less than 27 weeks GA
    - Erythropoietin 1200 U/Kg/week
    - Caffeine
    - Parenteral nutrition with fluids 70cc/K/d handled based on diuresis > 1cc/Kg/hour
        - Glucose 4mg/K/min
        - Protein 4 g/k/d
        - Lipids 3 g/K/d
- Trophic feeding (1-3 mL q. 3 hours)
- Probiotics

We design an observational cohort study and include patient born <30 weeks of GA, inborn or outborn less than 2 days old, that survived at least 3 days and had aneuroimaging taken. We compared tree different cohorts: Main cohort were cases in which the new protocol had been implement from oct 2017 until June 2022. Second group was and historical cohort from 2010 until oct 2017 managed with the old protocol. Three cohort consisted in all cases available from the 2018 -2020 EpicLatino registry (excluding our cases).

 doi:10.20944/preprints202112.0258.v2

We defined Grade 1 and 2 hemorrhage if there is hemorrhage in the germinal matrix and/or ventricles, without intraventricular dilation or periventricular hemorrhage. Grade 3 and 4 when there is ventricular dilation or hemorrhage outside the ventricles. Other parameters collected were birthweight, gestational age (GA), sex, inborn/outborn status, prenatal corticosteroids, vaginal delivery/ C-section, Apgar at 5´, treated patent ductus arteriosus (PDA).

All the parameters were compared within the three time periods using Chi-square test by Fischer's exact method or a Kruskal-Wallis equality-of-populations, depending on the type of variable. A logistic regression model was performed for the high-risk variables for IVH described in the literature and for those that were significant in the univariate model we used the EpicLatino group as the basal risk factor and the other variable´s Odds Ratio (OR) and 95% confidence interval (CI) were calculated.

Results

The study group consisted of 64 cases in the protocol group, 123 form the historic cohort and 1029 form the EpicLatino registry. Anthropometric and demographic characteristics are shown in table 1 and the IVH incidence in Table 2. As shown, prenatal corticosteroids, vaginal delivery/C section, PDA (treated) and Apgar at 5´were statistically significant.

Of the protocol group there were 4 cases with grade 1-2 hemorrhage (p 0.001) and 6 with grade 3-4 (p 0.021). In all the six cases of grade 3-4 hemorrhage, babies had very traumatic deliveries some with multiples hematomas to the head, body, and extremities.

The logistic regression model (Table 3 and Figure 1). The prenatal corticosteroids were not included in this logistic regression model due to an important number of cases with missing data in the EpicLatino database.

Discussion

The hemorrhage during delivery is well described[16] and must be prevented by the obstetric team, and cannot be prevented by a postnatal management.

The anthropometric and demographic characteristics that were statistically significantly different in some parameters could explain some of the difference in the intraventricular hemorrhagic results, as seen in the logistic regression model (see Table 3 and Figure 1). Low use of prenatal corticosteroids increases the risk of IVH,[11] and can explain in part the increased risk of IVH in the EpicLatino group, but due to a large amount of missing data, it could not be including in the

 doi:10.20944/preprints202112.0258.v2

logistic regression model. There is no discussion that increased gestational age protects against IVH, nevertheless, the gestational age distribution is symmetrical in all the groups. The vaginal delivery risk results may favor the study group (7.8% of vaginal deliveries), specially compared to EpicLatino (28.1% vaginal deliveries)[7] as verified by the logistic regression analysis.

The incidence of PDA could not be used as a reliable parameter since there is no information in the EpicLatino database witch very premature infants had an echocardiogram taken and when. The treated PDA selects the most severe cases of ductus and it is a risk factor that is corroborated in the logistic regression model. But on the other hand, the percentage of ductus treated in the study group 14.1% versus 32.9% in the EpicLatino group and 26.8% in the historical control which have high incidence of IVH, questions whether it is a selection of more severe cases, or, in fact, there is another factor such as fluid management in the first week of life the responsible for the lower incidence of IVH in the study group, but this information is not collected in the EpicLatino database.

Low Apgar score at 5´ is a surrogate for hypoxic insult or traumatic delivery and as expected, higher Apgar at 5´is associated independently to lower incidence of IVH as seen in the logistic regression model.

The very large difference in the incidence of IVH 1-2 or 3-4 in the study population is not completely explain by the difference in the factors described above. The logistic regression model helps to categorize the risk factors and the risk of IVH is robustly decreased in the study group independently, even if the other parameters as gestational age, vagina delivery, Apgar score at 5 minutes and treated PDA also are risk factors. As a limitation, since this is not a randomized control study, the variables affecting the incidence of IVH could not be control. Large randomized clinical trials are needed to confirm our findings.

Conclusion

The gentlehandling described in this work, with minimal manipulation and unnecessary strict lab managing seams to decrease the incidence of IVH and its severity in this population. Probably, modification of only one parameter as seen in randomized control studies will not change the incidence in IVH in a significant manner, but a bundle of modification in several parameter as seen in this quality improvement in practices may decrease the incidence of IVH.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202112.0258.v2

Table 1. Anthropometric and demographic characteristics

At Birth	Nov 2017-2022 July Protocol Cohort	2010-2017 Oct Historic Cohort	2018-2020 EpicLatino	P*
	n (%)	n (%)	n (%)	
n	64	123	1029	
Weight (gr)				
< 500	2 (3.1)	1 (0.8)	6 (0.6)	0.077
500-749	12 (18.8)	12 (9.7)	153 (14.9)	
750-999	14 (21.9)	49 (40.0)	338 (32.9)	
1000-1249	22 (34.4)	35 (28.5)	356 (34.6)	
1250-1499	13 (20.3)	23 (18.7)	145 (14.1)	
1500-2499	1 (1.6)	3 (2.4)	35 (2.9)	
Gestational age (w)				
<23	0 (0)	0 (0)	2 (0.2)	0.007
23	0 (0)	0 (0)	10 (1.0)	
24	1 (1.6)	2 (1.6)	50 (4.9)	
25	5 (7.8)	12 (9.7)	83 (8.1)	
26	6 (9.4)	12 (9.7)	38 (31.5)	
27	9 (14.1)	29 (23.6)	44 (21.7)	
28	11 (17.2)	28 (22.8)	47 (23.2)	
29	32 (50.0)	40 (32.5)	48 (23.7)	
Sex				
Male	38 (59.4)	70 (56.9)	554 (53.8)	0.966
Inborn	61 (95.3)	122 (99.2)	968 (94.7)	0.057
Prenatal corticosteroids	60 (93.8)	114 (92.7)	728 (70.7)$^{\beta}$	0.0001

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202112.0258.v2

At Birth	Nov 2017-2022 July Protocol Cohort	2010-2017 Oct Historic Cohort	2018-2020 EpicLatino	P*
	n (%)	n (%)	n (%)	
Vaginal delivery/ C section	5 (7.8) 59 (92.2)	9 (7.3) 114 (92.7)	289 (28.1) 738 (71.9)	<0.0001
Apgar 5´ (mean ±SD)	7.9 (1.1)	8.0 (1.1)	7.5 (1.6)	0.0113**
Deaths ≥ 3 days	13 (20.3)	36 (29.3)	260 (25.3)	0.396
PDA (treated)	9 (14.1)	33 (26.8)	338 (32.9)	0.004

ROM: rupture of membranes, PDA (treated): treated patent ductus arteriosus, CldelC: Clinica del Country.

*Chi-square test by Fischer's exact method

**Kruskal-Wallis equality-of-populations rank test

$^{\beta}$ 8.9% missing cases

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202112.0258.v2

Table 2. IVH Results

IVH	Nov 2017-2022 July Protocol Cohort	2010-2017 Oct Historic Cohort	2018-2020 EpicLatino	P*
	n (%)	n (%)	n (%)	
	64	123	1029	
NORMAL	54 (84.4)	82 (66.7)	536 (52.1)	<0.0001
IVH I-II	4 (6.3)	25 (20.3)	263 (25.6)	0.001
IVH III-IV	6 (9.4)	16 (13.0)	208 (20.2)	0.021

CldelC: Clinica del Country.

*Chi-square test by Fischer's exact method

Nov: November, Oct: October

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202112.0258.v2

Table 3: Logistic Regression: IVH risk factors

Factor	OR	P values	CI 95%
EpicLatino	1.00	Ref	
Historic Cohort	0.67	0.060	0.45 - 1.02
Protocol Cohort	0.27	**<0.001**	0.13 - 0.54
Gestational Age (weeks)	0.81	**<0.001**	0.74 - 0.88
Vaginal Delivery	1.95	**<0.001**	1.46 - 2.59
Treated PDA	1.33	**0.045**	1.02 - 1.73
5´ Abgar score	0.86	**0.001**	0.79 - 0.94

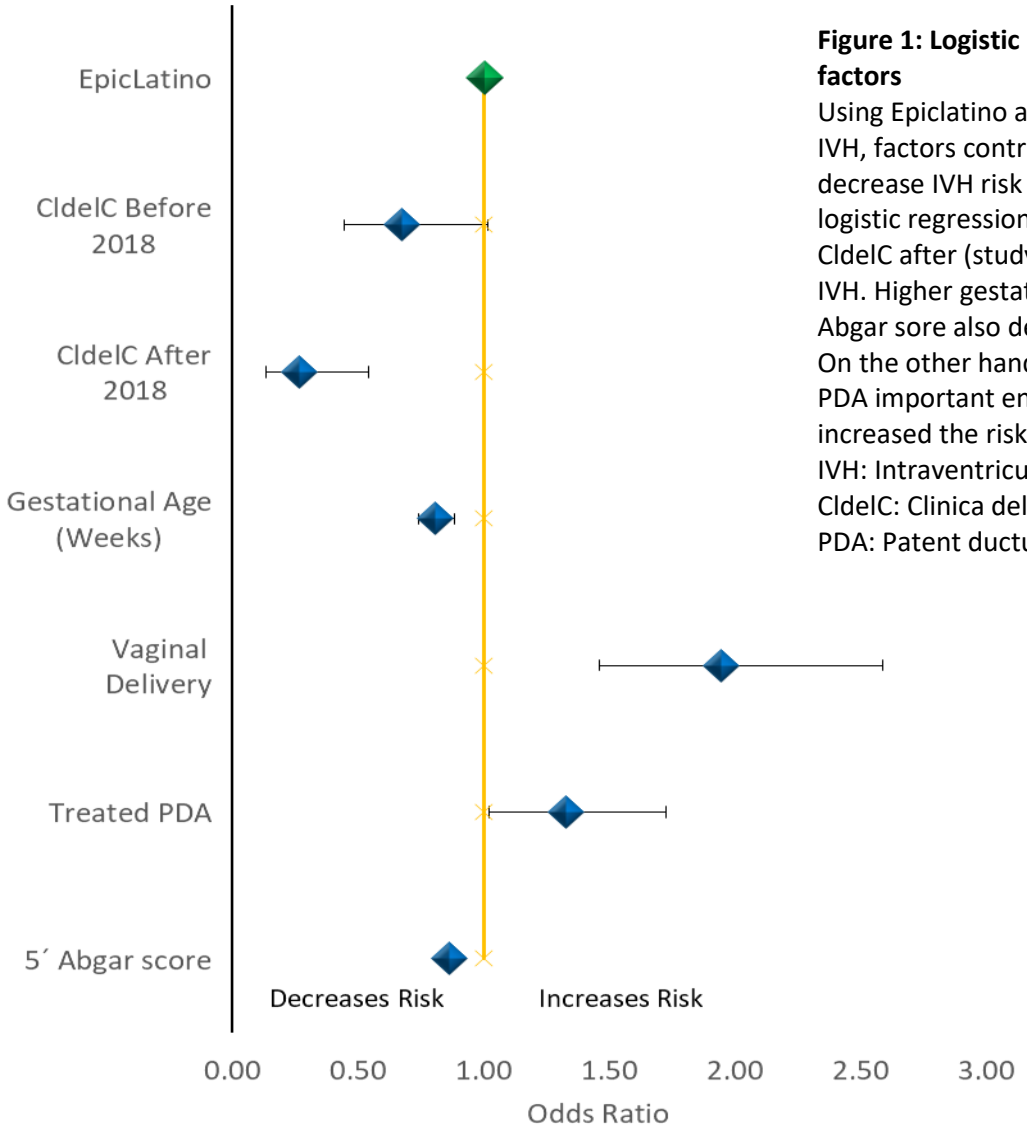

Figure 1: Logistic Regression: IVH risk factors
Using Epiclatino as a reference basal risk for IVH, factors contributing to increase or decrease IVH risk were calculated using a logistic regression model.
CldelC after (study group) has lower risk of IVH. Higher gestational age and higher 5´ Abgar sore also decreases the risk.
On the other hand, vaginal delivery, and PDA important enough to need treatment increased the risk of IVH.
IVH: Intraventricular hemorrhage
CldelC: Clinica del Country
PDA: Patent ductus arteriosus

Acknowledgment: The authors are indebted to all parents and their infants. We thank all nurses and doctors and study centers who participate in the Database. The participating EpicLatino Units were: Gonzalez, D: Clinica Latino, Cuenca, Ecuador. Africano M: Clinica Materno Infantil San Luis, Bucaramanga, Colombia. Jara E: Clínica Santa Bárbara, Quito, Ecuador. Gonzalez E: Clínica Somer, Rio Negro, Colombia. Villegas C: Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosí, México. Torres S: Hospital Centro Policlinico del Olaya, Bogota, Colombia. Burbano CG: Hospital Civil de Ipiales, Ipiales, Colombia. Delgado V: Hospital de los Valles, Quito, Ecuador. Roge H: Hospital Español de Mendoza, Mendoza, Argentina. Arias D: Hospital San José, Bogotá, Colombia. Belzu MA. Hospital Dr. Florencio Escardó, Tigre, Argentina. Zambosco GA. La Plata, Argentina. Aguinaga F: Hospital Metropolitan, Quito, Ecuador. Alarcon C. Hospital Militar Central, Bogotá, Colombia. Castellanos JC: Hospital Regional Universitario de Colima, Colima, Mexico. Calero M: Hospital San Francisco de Quito, Quito, Ecuador. Cruz B: Hospital Prov. General Docente Riobamba, Riobamba, Ecuador. Martinini MI: Maternidad Nuestra Sra. de las Mercedes, Tucuman, Argentina. Fernandez M: Hospital Santisima Trinidad, Asunción, Paraguay. Duque N: St. Elisabeth Hospital. Lopez OJ: S.E.S Hospital de Caldas, Manizales, Colombia. Zambrano IR: Hospital General EISS de Manta, Manta, Ecuador. Barrera NP: Hospital Departamental San Vicente de Paul, Garzon, Huila, Colombia.

Reference

1. Leijser LM, de Vries LS. Preterm brain injury: Germinal matrix-intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. *Handb Clin Neurol*. 2019;162:173-199. doi:10.1016/B978-0-444-64029-1.00008-4
2. Hinojosa-Rodríguez M, Harmony T, Carrillo-Prado C, et al. Clinical neuroimaging in the preterm infant: Diagnosis and prognosis. *Neuroimage Clin*. 2017;16:355-368. doi:10.1016/j.nicl.2017.08.015
3. Tan AP, Svrckova P, Cowan F, Chong WK, Mankad K. Intracranial hemorrhage in neonates: A review of etiologies, patterns and predicted clinical outcomes. *Eur J Paediatr Neurol*. Jul 2018;22(4):690-717. doi:10.1016/j.ejpn.2018.04.008
4. Al-Abdi SY, Al-Aamri MA. A Systematic Review and Meta-analysis of the Timing of Early Intraventricular Hemorrhage in Preterm Neonates: Clinical and Research Implications. *J Clin Neonatol*. Apr 2014;3(2):76-88. doi:10.4103/2249-4847.134674
5. Al-Abdi SY, Al-Aamri MA. Timing of Intraventricular Hemorrhage in Preterm Neonates. *J Pediatr*. Aug 11 2021;doi:10.1016/j.jpeds.2021.07.063
6. Goswami IR, Abou Mehrem A, Scott J, Esser MJ, Mohammad K. Metabolic acidosis rather than hypo/hypercapnia in the first 72 hours of life associated with intraventricular hemorrhage in preterm neonates. *J Matern Fetal Neonatal Med*. Dec 18 2019:1-9. doi:10.1080/14767058.2019.1701649
7. Humberg A, Härtel C, Paul P, et al. Delivery mode and intraventricular hemorrhage risk in very-low-birth-weight infants: Observational data of the German Neonatal Network. *Eur J Obstet Gynecol Reprod Biol*. May 2017;212:144-149. doi:10.1016/j.ejogrb.2017.03.032
8. Hefti MM, Trachtenberg FL, Haynes RL, Hassett C, Volpe JJ, Kinney HC. A Century of Germinal Matrix Intraventricular Hemorrhage in Autopsied Premature Infants: A Historical Account. *Pediatr Dev Pathol*. 2016 Mar-Apr 2016;19(2):108-14. doi:10.2350/15-06-1663-OA.1
9. Vesoulis ZA, Flower AA, Zanelli S, et al. Blood pressure extremes and severe IVH in preterm infants. *Pediatr Res*. 01 2020;87(1):69-73. doi:10.1038/s41390-019-0585-3
10. Khanafer-Larocque I, Soraisham A, Stritzke A, et al. Intraventricular Hemorrhage: Risk Factors and Association With Patent Ductus Arteriosus Treatment in Extremely Preterm Neonates. Original Research. *Frontiers in Pediatrics*. 2019-October-22 2019;7(408)doi:10.3389/fped.2019.00408
11. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 12 25 2020;12:CD004454. doi:10.1002/14651858.CD004454.pub4
12. de Bijl-Marcus K, Brouwer AJ, De Vries LS, Groenendaal F, Wezel-Meijler GV. Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study. *Arch Dis Child Fetal Neonatal Ed*. Jul 2020;105(4):419-424. doi:10.1136/archdischild-2018-316692
13. EpicLatino. Epiclatino Repport 2018-2020. https://www.epiclatino.co/reportes/
14. Ryan M, Lacaze-Masmonteil T, Mohammad K. Neuroprotection from acute brain injury in preterm infants. *Paediatr Child Health*. Jul 2019;24(4):276-290. doi:10.1093/pch/pxz056
15. Carroll K, Kumar P, Prazad P, Mohammad K, Raghavan A, Wang H. Midline Head Positioning for Prevention of Intraventricular Hemorrhage (IVH) in Infants Born at 23-28 weeks gestation: a multicenter retrospective cohort stud. *Pediatrics*. 2019;144(2 MeetingAbstract):660-660. doi:10.1542/peds.144.2_MeetingAbstract.660
16. Lim J, Hagen E. Reducing Germinal Matrix-Intraventricular Hemorrhage: Perinatal and Delivery Room Factors. *Neoreviews*. 08 2019;20(8):e452-e463. doi:10.1542/neo.20-8-e452