Reunión Bibliografica.

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Effect of High-Dose Erythropoietin on Blood Transfusions in Extremely Low Gestational Age Neonates Post Hoc Analysis of a Randomized Clinical Trial

Suul S, et al, for the Preterm Erythropoietin Neuroprotection Trial Consortium.

JAMA Pediatr. doi:10.1001/jamapediatrics.2020.2271

- **OBJECTIVES** To determine whether high-dose erythropoietin given within 24 hours of birth through postmenstrual age of 32 completed weeks will decrease the need for blood transfusions.
- **INTERVENTIONS** In this post hoc analysis, erythropoietin, 1000 U/kg, or placebo was given every 48 hours for 6 doses, followed by 400 U/kg or sham injections 3 times a week through postmenstrual age of 32 weeks.
- **MAIN OUTCOMES AND MEASURES** Need for transfusion, transfusion numbers and volume, number of donor exposures, and lowest daily hematocrit level are presented herein.
- **DESIGN, SETTING, AND PARTICIPANTS** The Preterm Erythropoietin Neuroprotection Trial (PENUT) is a randomized, double-masked clinical trial with participants enrolled at 19 sites consisting of 30 neonatal intensive care units across the United States. Participants were born at a gestational age of 24 weeks (0-6 days) to 27 weeks (6-7 days). Exclusion criteria included conditions known to affect neurodevelopmental outcomes. Of 3266 patients screened, 2325 were excluded, and 941 were enrolled and randomized to erythropoietin (n = 477) or placebo (n = 464). Data were collected from December 12, 2013, to February 25, 2019, and analyzed from March 1 to June 15, 2019.

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RESULTS:

- A total of 936 patients (488 male [52.1%]) were included in the analysis
- Gestational Age: Mean 25.6 (1.2) weeks
- Birth weight: Mean 799 (189) g.
- Erythropoietin treatment (vs placebo)
  - number of transfusions (unadjusted mean [SD], 3.5 [4.0] vs 5.2 [4.4]), with a relative rate (RR) of 0.66 (95%CI, 0.59-0.75)
  - the cumulative transfused volume (mean [SD], 47.6 [60.4] vs 76.3 [68.2] mL), with a mean difference of −25.7 (95%CI, 18.1-33.3) mL
  - donor exposure (mean [SD], 1.6 [1.7] vs 2.4 [2.0]), with an RR of 0.67 (95%CI, 0.58-0.77).
  - hematocrit level at 33 weeks in erythropoietin-treated vs placebo-treated cohorts, 36.9%[5.5%] vs 30.4%[4.6%] ($P < .001$).
  - Of 936 infants, 160 (17.1%) remained transfusion free at the end of 12 postnatal weeks, including 43 in the placebo group and 117 in the erythropoietin group ($P < .001$).

- Erytropoietin:
- Participants received erythropoietin, 1000U/kg per dose, or placebo intravenously every 48 hours for 6 doses, followed by maintenance dosing of 400U/kg per dose by subcutaneous injection or sham injections 3 times a week until postmenstrual age (PMA) of 32 weeks (6-7 days).
- Iron: when enteral feedings were started, use of a standard iron containing formula if breast milk was unavailable. When participants reached an enteral intake of 60 mL/kg/d and were at least 7 days of age, a starting enteral iron intake of 3mg/kg/d was recommended. Iron intake should be increased to 6mg/ kg/d when infants achieved an enteral intake of 100mL/kg/d.
- The serum ferritin level or the ratio of zinc protoporphyrin to heme (ZnPP:H) should be checked at 14and42days,with iron dosing adjusted accordingly.
- If participants were not able to tolerate enteral feedings, they should receive maintenance iron supplementation parenterally (3mg/kg/wk, adjusted based on iron indices).

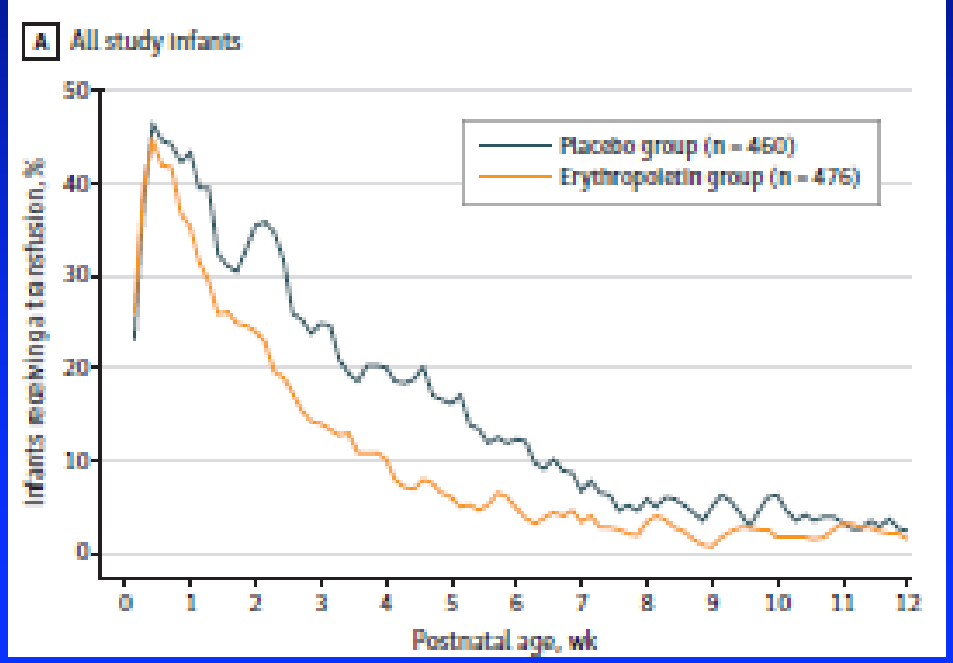
- Transfusion Guidelines:
- Because no consensus recommendations exist for transfusions in critically ill neonates, each site followedtheir own procedures for pRBC transfusion. Five sites did not use transfusion guidelines. The remaining sites used guidelines but differed in transfusion triggers, blood volume transfused per transfusion, and pRBC preservative solutions

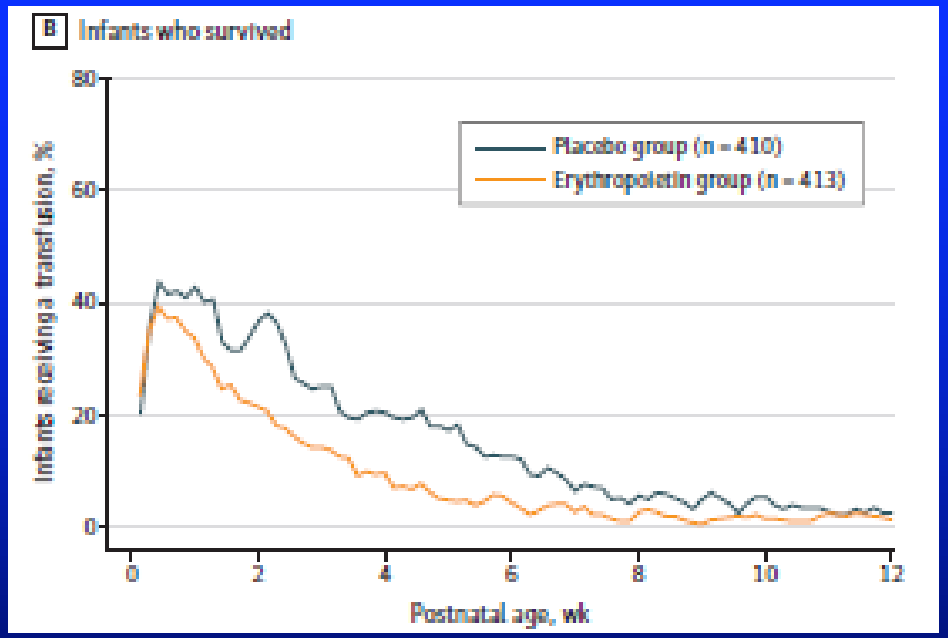
Characteristic	No. of infants	No. (%) with any pRBC transfusion in the first 12 weeks	*P* value[a]
Randomization			
Erythropoietin	476	359 (75.4)	<.001
Placebo	460	417 (90.7)	

Characteristic	No. of infants	No. (%) with any pRBC transfusion in the first 12 weeks	*P* value[a]
Cesarean delivery			
Yes	651	559 (85.9)	<.001
No	285	217 (76.1)	
Delayed cord clamping[l]			
Yes	318	245 (77.0)	.001
No	362	317 (87.6)	

Characteristic	No. of infants	No. (%) with any pRBC transfusion in the first 12 weeks	*P* value[a]
Risk of infection[e]			
Yes	689	565 (82.0)	.001
No	247	211 (85.4)	
Gestational age at birth, wk			
24	232	230 (99.1)	<.001
25	245	229 (93.5)	
26	221	173 (78.3)	
27	238	144 (60.5)	
Weight <10th percentile[l]			
Yes	147	133 (90.5)	<.001
No	785	639 (81.4)	
Occipital frontal circumference <10th percentile[k]			
Yes	161	145 (90.1)	<.001
No	752	612 (81.4)	
Apgar score at 5 min <5[l]			
Yes	189	182 (96.3)	<.001
No	744	591 (79.4)	
Intracranial hemorrhage before first dose			
Yes	197	174 (88.3)	.02
No	739	602 (81.5)	

Figure 2. Transfusion Rate by Treatment Group and Survival Status





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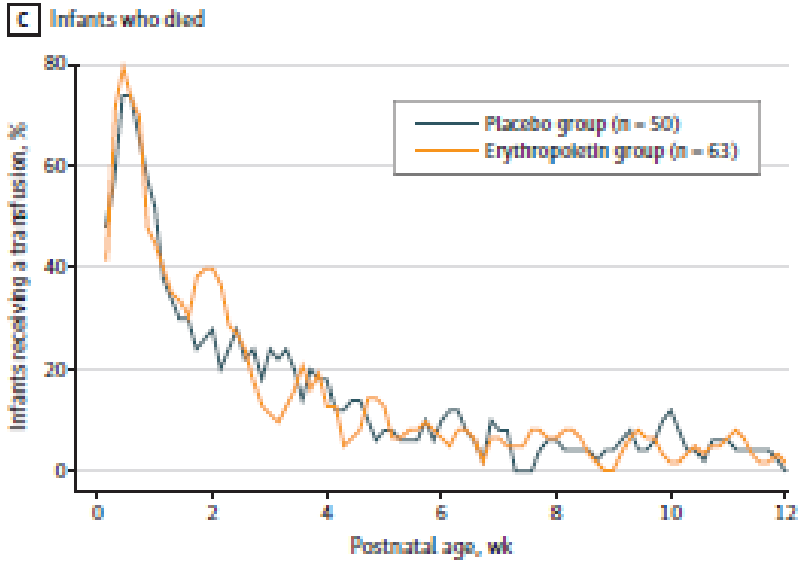
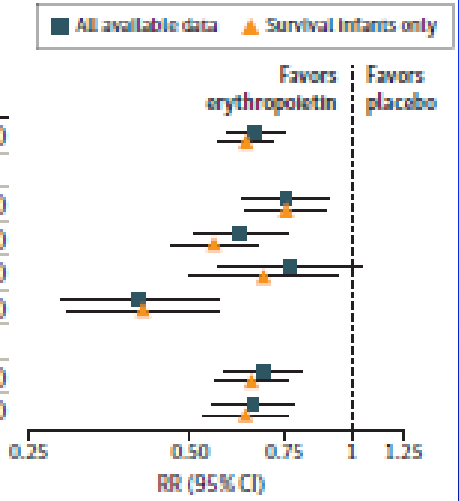


Moving 3-day transfusion rates (ie, proportion of infants receiving a transfusion for every 3-day window) by treatment group were calculated for all infants (A [n = 936]), those who survived (B [n = 823]), and those who died (C [n = 113]).

Figure 3. Transfusion Exposures by Treatment Group

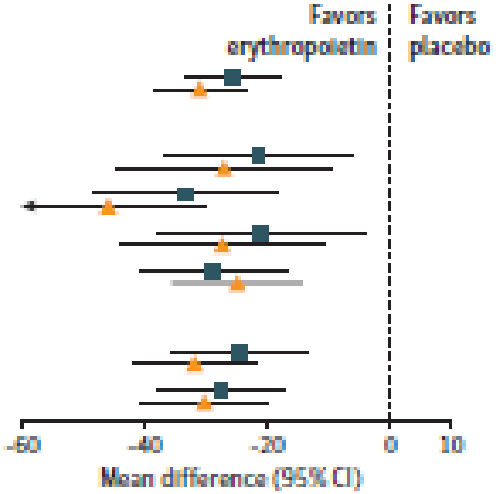
A No. of pRBC transfusions

Source	Mean (SD) No. of transfusions: Erythropoietin group	Placebo group	RR (95% CI)
Overall	3.5 (4.0)	5.2 (4.4)	0.66 (0.59-0.75)
By gestational age at birth, wk			
24 (n = 232)	6.4 (4.5)	7.8 (4.8)	0.75 (0.62-0.91)
25 (n = 245)	3.8 (2.8)	6.0 (4.2)	0.62 (0.51-0.75)
26 (n = 221)	3.0 (4.5)	3.6 (3.4)	0.77 (0.57-1.04)
27 (n = 238)	1.1 (1.8)	3.0 (3.1)	0.40 (0.29-0.56)
By sex			
Female (n = 448)	3.2 (3.8)	5.0 (4.3)	0.66 (0.55-0.78)
Male (n = 488)	3.7 (4.1)	5.5 (4.5)	0.68 (0.58-0.80)



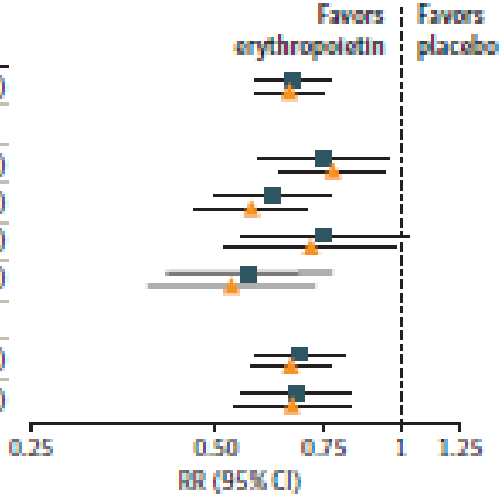
B Cumulative volume of pRBC transfusions

Source	Mean (SD) No. of transfusions: Erythropoietin group	Placebo group	Mean difference (95% CI)
Overall (n = 936)	47.6 (60.4)	76.3 (68.2)	-25.66 (-33.26 to -18.07)
By gestational age at birth, wk			
24 (n = 232)	77.5 (66.1)	99.7 (67.0)	-21.42 (-36.45 to -6.38)
25 (n = 245)	52.5 (49.6)	87.3 (70.5)	-33.32 (-48.47 to -18.17)
26 (n = 221)	44.6 (72.8)	62.2 (69.2)	-20.97 (-37.77 to -4.18)
27 (n = 238)	21.2 (38.8)	51.5 (52.6)	-28.73 (-40.45 to -17.00)
By sex			
Female (n = 448)	38.7 (51.9)	69.8 (65.9)	-27.53 (-37.56 to -17.50)
Male (n = 488)	55.2 (66.0)	82.8 (70.0)	-24.53 (-35.55 to -13.51)



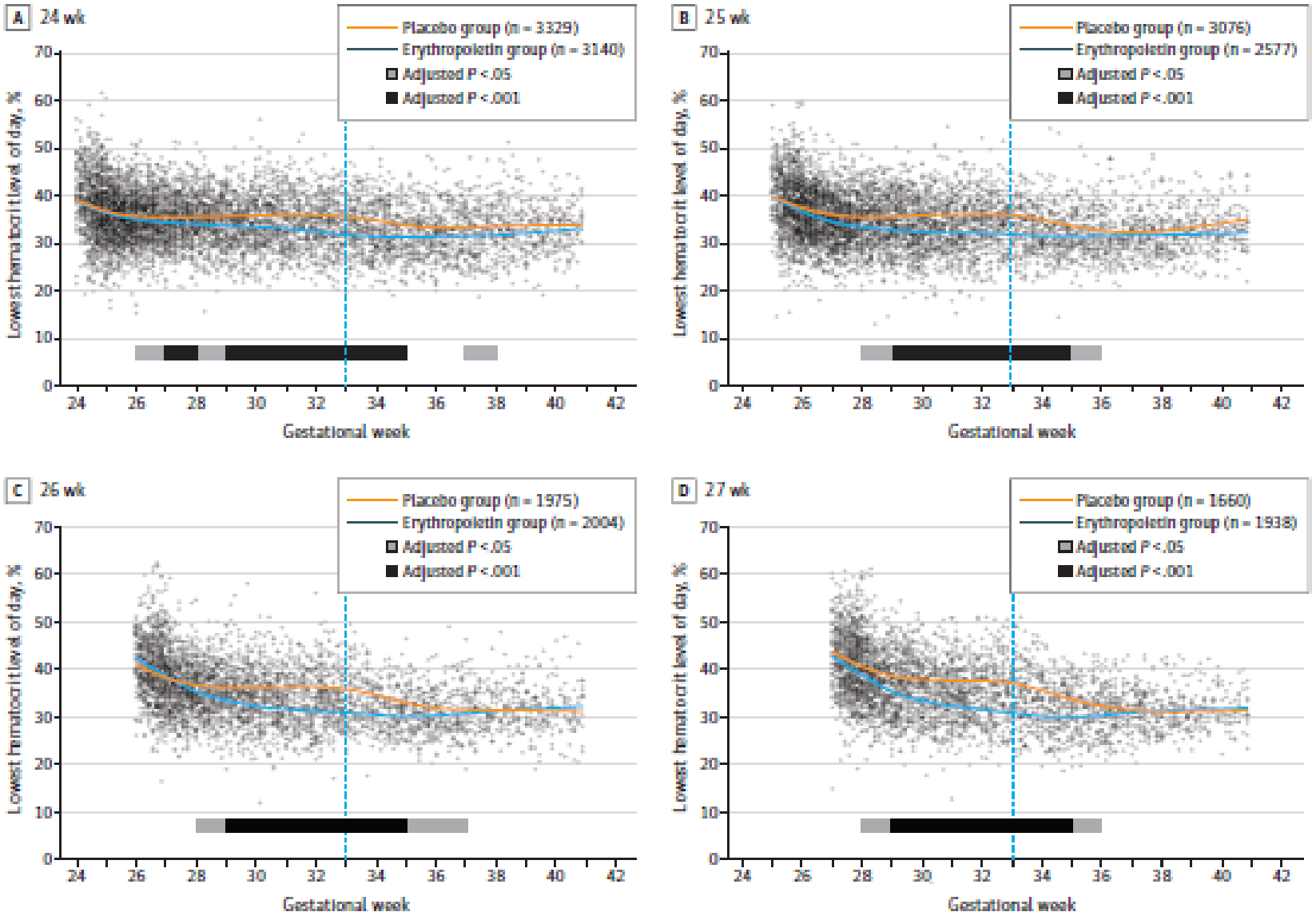
C Donor exposure

Source	Mean (SD) donor exposure: Erythropoietin group	Placebo group	RR (95% CI)
Overall (n = 936)	1.6 (1.7)	2.4 (2.0)	0.67 (0.58-0.77)
By gestational age at birth, wk			
24 (n = 232)	2.5 (1.8)	3.0 (2.3)	0.75 (0.59-0.96)
25 (n = 245)	1.7 (1.3)	2.8 (2.1)	0.62 (0.50-0.77)
26 (n = 221)	1.4 (2.0)	1.8 (1.5)	0.75 (0.55-1.02)
27 (n = 238)	0.8 (1.2)	1.6 (1.5)	0.57 (0.41-0.77)
By sex			
Female (n = 448)	1.5 (1.9)	2.2 (2.0)	0.67 (0.55-0.83)
Male (n = 488)	1.6 (1.5)	2.5 (2.0)	0.69 (0.58-0.81)



The number of packed red blood cell (pRBC) transfusions (A [4061 records]), cumulative volume of pRBC transfusions (B [4052 records]), and donor exposure (C [3808 records]) were compared between treatment groups. Mean values were compared using generalized estimating equation models clustering on same-birth siblings, adjusted for gestational age and site. Relative rate (RR) of less than 1.00 favored the erythropoietin group.

Figure 4. Lowest Daily Hematocrit Level Over Time by Gestational Age at Birth



Mean weekly values by treatment group were compared using generalized estimating equation models clustering on same-birth siblings and adjusting for recruitment site. Significance was shown by $P < .05$ and $P < .001$ bars. The .001 level was chosen as an approximation to a conservative Bonferroni correction (.05 level divided by the total number of tests performed on the weekly data sets). Blue vertical line indicates week 33, at which the last erythropoietin or placebo dose was given.

Association Between Congenital Cytomegalovirus and the Prevalence at Birth of Microcephaly in the United States.

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- **OBJECTIVE**:
  - To evaluate the association between cCMV and the prevalence at birth of microcephaly in the United States.
- **DESIGN, SETTING, AND PARTICIPANTS:**
  - This population-based cohort study included pregnant women and their newborns identified in 2 insurance claims databases from the United States: Medicaid Analytic eXtract (January 1, 2000, to December 31, 2013) and IBM Research MarketScan, a database for employer-sponsored private health insurance (January 1, 2011, to September 30, 2015). All pregnancies that resulted in live births in women with full health benefits were included. Analysis began June 2016 and ended May 2020.
- **EXPOSURES:**
  - congenital cytomegalovirus infection documented in inpatient or outpatient newborn claims records.
- **MAIN OUTCOMES AND MEASURES:**
  - The primary outcome was microcephaly at birth documented in inpatient or outpatient newborn and/or maternal claims records. Cases with chromosomal abnormalities or neural tube defects were excluded. The association between cCMV and microcephaly was estimated in the pooled cohort using prevalence ratios (PRs) and 95%CIs.

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- RESULTS:
  - In the pooled cohort of 2 338 580 pregnancies (2 075 410 pregnancies [88.7%] were among women younger than 35 years), 336 infants (0.014%) had a cCMV diagnosis.
  - The prevalence of microcephaly among newborns with and without a cCMV diagnosis was 655 and 2.8 per 10 000 live births, respectively (PR, 232; 95%CI, 154-350).
  - After restricting to CMV-tested newborns (572 [0.024%]) to correct for preferential testing of infants with microcephaly, the PR was 15 (95%CI, 5.2-41). However, this PR is biased if other cCMV-related outcomes (eg, hearing loss) trigger testing because cCMV prevalence in tested infants, with ([46%]) or without microcephaly (22 of 559 [3.9%]), would overestimate that in the source population. Therefore, the prevalence of cCMV in overall infants with microcephaly (22 of 669 [3.2%]) was compared with that from an external unbiased sample of US infants screened at birth (449 of 100 332 [0.45%]) to estimate a PR of 7.4 (95%CI, 4.8-11.5) as a conservative lower bound.

- CONCLUSIONS AND RELEVANCE:
  - Congenital cytomegalovirus infection increases the prevalence of microcephaly at birth by at least 7-fold. Prevention of CMV infection during pregnancy might substantially reduce the number of newborns with microcephaly and other cCMV-related outcomes in the United States.

Key Points

Question What is the association of congenital cytomegalovirus with the prevalence at birth of microcephaly in the United States?

Findings In this population-based cohort study of 2.3 million pregnancies identified in health care data from 2000 to 2015 in the United States, the prevalence of microcephaly was 2.1 to 7.7 per 10 000 live births, depending on case definition. Congenital cytomegalovirus diagnosis was the strongest measured risk factor for microcephaly, increasing the risk by at least 7-fold.

Meaning Congenital cytomegalovirus is an important cause of microcephaly and other newborn neurologic outcomes in the United States and warrants greater attention from public health and medical fields.

Table 2. Prevalence at Birth of Microcephaly and Other Neurologic Outcomes Recorded Within First 90 Days of Life Among Infants With and Without a cCMV Diagnosis in a Cohort of Pregnancies Nested Within Pooled Medicaid Analytic eXtract (2000-2013) and MarketScan (2011-2015) Databases

Outcome	Total, No.	No. (%)		Summary prevalence ratio (95% CI)[a]
		cCMV diagnosis (n = 336)	No cCMV diagnosis (n = 2 338 244)	
Microcephaly	679	22 (6.5)	657 (0.03)	232 (154-350)
Neonatal seizures	5922	<11[b]	NA	8 (4-17)
Hearing loss	4605	28 (8.3)	4577 (0.2)	46 (31-68)
Chorioretinitis or eye anomalies[c]	1025	<11[b]	NA	69 (37-128)

Abbreviations: cCMV, congenital cytomegalovirus; NA, not applicable.

[a] Prevalence ratio of outcome among infants with a cCMV diagnosis divided by that in those without a cCMV diagnosis.

[b] Cell contains fewer than 11 individuals. Therefore, to provide summary prevalence ratios while maintaining anonymity of participants, no additional frequency numbers are provided for this row.

[c] Chorioretinitis and eye anomalies were combined owing to small case counts.

Table 3. Prevalence at Birth of Select Central Nervous System Outcomes Recorded Within First 90 Days of Life Among Infants With and Without a Diagnosis of Microcephaly in a Cohort of Pregnancies Nested Within Pooled Medicaid Analytic eXtract (2000-2013) and MarketScan (2011-2015) Databases

Outcome	Total, No.	No. (%)		Summary prevalence ratio (95% CI)[a]
		Microcephaly diagnosis (n = 679)	No microcephaly diagnosis (n = 2 337 901)	
Neonatal seizures	5922	44 (6.5)	5878 (0.2)	25 (19-34)
Hearing loss	4605	14 (2.1)	4591 (0.2)	11 (6.3-18)
Chorioretinitis or eye anomalies[b]	1025	13 (1.9)	1012 (0.04)	45 (26-77)

[a] Prevalence ratio of outcome among infants with microcephaly compared with infants without microcephaly.

[b] Chorioretinitis and eye anomalies were combined owing to small case counts.

Association Between Epidural Analgesia During Labor and Risk of Autism Spectrum Disorders in Offspring.

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- OBJECTIVE:
  - To assess the association between maternal LEA exposure and risk of autism spectrum disorders (ASDs) in offspring.
- DESIGN, SETTING, AND PARTICIPANTS:
  - Data for this retrospective longitudinal birth cohort study were derived from electronic medical records from a population-based clinical birth cohort. A total of 147 895 singleton children delivered vaginally between January 1, 2008, and December 31, 2015, in a single integrated health care system were included. Children were followed up from the age of 1 year until the first date of the following occurrences: clinical diagnosis of ASD, last date of health plan enrollment, death, or the study end date of December 31, 2018.
- EXPOSURES:
  - Use and duration of LEA.
- MAIN OUTCOMES AND MEASURES:
  - The main outcome was clinical diagnosis of ASD. Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) of ASD associated with LEA exposure.

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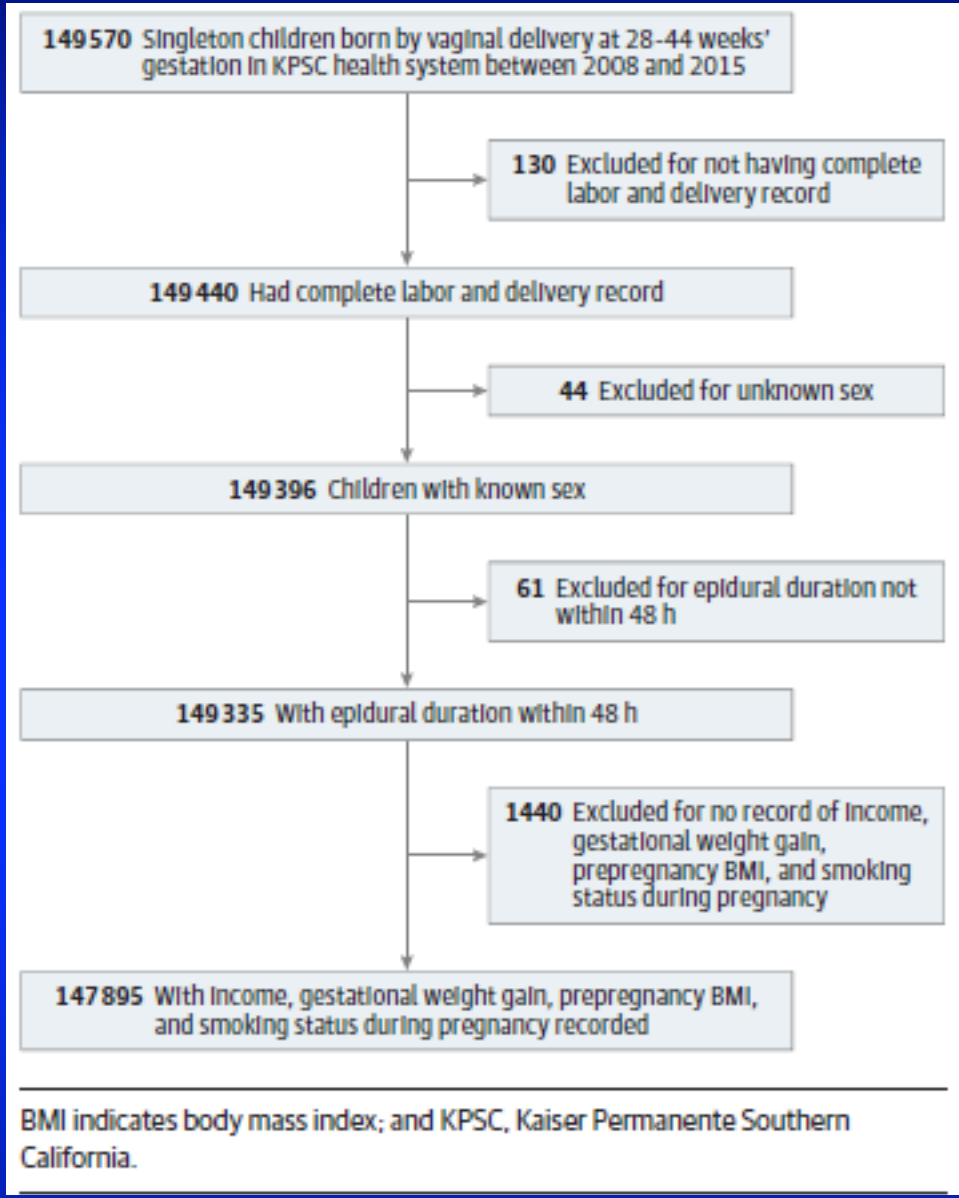
Key Points

Question Is there an association between maternal labor epidural analgesia given for vaginal delivery and risk of autism spectrum disorders in children?

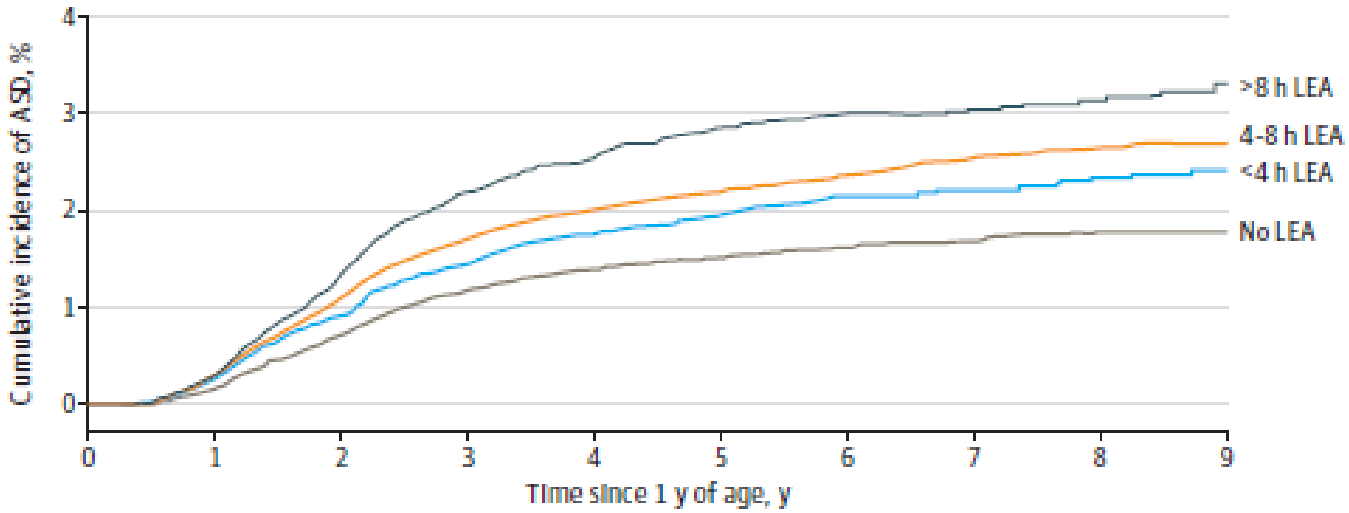
Findings In this multiethnic population-based clinical birth cohort that included 147 895 children, autism spectrum disorders were diagnosed in 1.9% of the children delivered vaginally with epidural analgesia vs 1.3% of the children delivered vaginally without the exposure, a 37% relative increase in risk that was significant after adjusting for potential confounders.

Meaning This study suggests that exposure to epidural analgesia for vaginal delivery may be associated with increased risk of autism in children; further research is warranted to confirm the study findings and understand the potential mechanisms.



BMI indicates body mass index; and KPSC, Kaiser Permanente Southern California.

Figure 2. Unadjusted Cumulative Incidence of Autism Spectrum Disorder (ASD) by Duration of Labor Epidural Anesthesia (LEA)



No. at risk										
No LEA	38176	34965	31723	25426	20296	16268	12889	9882	6964	4079
<4 h LEA	32433	29658	26841	21315	16715	12883	9472	6578	3984	1645
4-8 h LEA	50248	45628	41260	32259	24746	18676	13487	9087	5411	2233
>8 h LEA	27038	24646	22165	16689	12437	9028	6299	4092	2393	1003

Table 2. Associations Between Labor Epidural Analgesia Use at Delivery and Risk of ASD in Offspring

Characteristic	No. with ASDs/total No.	Hazard ratio (95% CI)	
		Bivariable[a]	Adjusting for covariates[b]
Labor epidural analgesia			
No	485/38 176	1 [Reference]	1 [Reference]
Yes	2039/109 719	1.48 (1.34-1.65)	1.37 (1.23-1.53)
Duration of labor epidural analgesia			
No labor epidural analgesia	485/38 176	1 [Reference]	1 [Reference]
<4 h	527/32 433	1.28 (1.12-1.46)	1.33 (1.17-1.53)
4-8 h	911/50 248	1.46 (1.29-1.64)	1.35 (1.20-1.53)
>8 h	601/27 038	1.78 (1.57-2.03)	1.46 (1.27-1.69)
Linear trend (per 4 h)[c]	2039/109 719	1.11 (1.07-1.15)	1.05 (1.01-1.09)

Abbreviation: ASD, autism spectrum disorder.

[a] Labor epidural analgesia was analyzed individually where only birth year was adjusted in the model.

[b] Covariates included birth year, maternal age at delivery, parity, race/ethnicity, educational level, household income, history of comorbidity, diabetes during pregnancy, smoking during pregnancy, preeclampsia or eclampsia, prepregnancy body mass index, gestational weight gain, gestational age at delivery, birth weight, and medical center.

[c] Linear trend is defined as the duration of labor epidural analgesia as a continuous variable within the labor epidural analgesia group.

Table 3. Associations Between Labor Epidural Analgesia Use at Delivery and Risk of Autism Spectrum Disorders in Offspring

Exposure	Excluding preterm birth (<37 wk)[a]		Excluding children with birth defects[b]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Labor epidural analgesia				
No	1 [Reference]	Not applicable	1 [Reference]	Not applicable
Yes	1.40 (1.25-1.57)	<.001	1.46 (1.29-1.65)	<.001

[a] There were 8805 children excluded owing to a gestational age of less than 37 weeks. Adjustments were made for birth year, maternal age at delivery, parity, race/ethnicity, educational level, household income, history of comorbidity, diabetes during pregnancy, smoking during pregnancy, preeclampsia or eclampsia, prepregnancy body mass index, gestational weight gain, gestational age at delivery, birth weight, and medical center.

[b] There were 18 606 children excluded owing to the presence of birth defects at birth. Adjustments were made for birth year, maternal age at delivery, parity, race/ethnicity, educational level, household income, history of comorbidity, diabetes during pregnancy, smoking during pregnancy, preeclampsia or eclampsia, prepregnancy body mass index, gestational weight gain, gestational age at delivery, birth weight, and medical center.

- Espontánea en aproximadamente el 10 – 30 seg en el 85% de los RNT
- 10% la inician después de secar y estimular
- 5% de los RNT requieren VPP
- 2% Son intubados
- 0,1% Requiere masaje cardíaco
- 0.05% Compresiones torácicas + adrenalina

- Anticipation and Preparation The keys to successful neonatal resuscitation include:
  - assessment of perinatal risk
  - a system to rapidly assemble team members with skills that are appropriate to the anticipated need for resuscitation on the basis of that risk.
  - an organized resuscitation area that ensures immediate access to all needed supplies and equipment
  - the standardization of behavioral skills that foster optimal teamwork and communication.
- These treatment recommendations (below) are unchanged from 2010
  - When an infant without antenatally identified risk factors is delivered at term by cesarean delivery under regional anesthesia, a provider capable of performing assisted ventilation should be present at the delivery. It is not necessary for a provider skilled in neonatal intubation to be present at that delivery.
- Briefing and debriefing:
  - We conclude that briefing or debriefing may improve short-term clinical and performance outcomes for infants and staff. The effects of briefing or debriefing on long-term clinical and performance outcomes are uncertain.

- Warming: Recommendations are unchanged from 2015.
- Among newborn preterm infants of less than 32 weeks' gestation under radiant warmers in the hospital delivery room, we suggest using a combination of interventions that may include environmental temperature 23 C to 25 C, warm blankets, plastic wrapping without drying, cap, and thermal mattress to reduce hypothermia (temperature less than 36.0 C) on admission to NICU (weak recommendation, very low-certainty evidence).
- We suggest that hyperthermia (greater than 38.0 C) be avoided because it introduces potential associated risks (weak recommendation, very low-certainty evidence).
- **Suctioning:** Oropharyngeal suctioning does not impact liquid removal from the lung. The procedure can have serious side effects. It is possible that nasopharyngeal suctioning may result in vagal-induced bradycardia as well as increased risk of infection. The procedure may take significant time to complete. Suctioning may delay initiation of ventilation in nonbreathing infants.
- Newborns who received suctioning compared with a control group had significantly lower oxygen saturation through the first 6 minutes of life and took longer to reach a normal saturation range. There is a concern that suctioning may have serious additional consequences, such as irritation to mucous membranes and increased risk of iatrogenic infection, bradycardia, apnea, hypoxemia and arterial oxygen desaturation, hypercapnia, impaired cerebral blood flow regulation, increased intracranial pressure, and development of subsequent neonatal brain injury.
- **Treatment Recommendation is unchanged from 2010. Routine intrapartum oropharyngeal and nasopharyngeal suctioning for newborn infants with clear or meconium-stained amniotic fluid is no longer recommended.**

- **Tracheal Intubation and Suction of Nonvigorous Meconium- Stained Newborns**
  - 5-15% de los RN tienen LA teñido con Meconio. Es más frecuente en RN no vigorosos.
  - 3-5% de los RN con LA teñido con meconio desarrollan SAM
- **Treatment Recommendations:**
  - For nonvigorous newborn infants delivered through meconium-stained amniotic fluid, we suggest against routine immediate direct laryngoscopy with or without tracheal suctioning compared with immediate resuscitation without direct laryngoscopy (weak recommendation, low-certainty evidence). Meconium-stained amniotic fluid remains a significant risk factor for receiving advanced resuscitation in the delivery room. Rarely, an infant may require intubation and tracheal suctioning to relieve airway obstruction.

The NLS Task Force considered that the procedure of laryngoscopy and suctioning with or without tracheal intubation is invasive and has potential to harm, particularly if initiation of ventilation is delayed. This, together with the evidence of no benefit of routine tracheal suctioning, led the task force to suggest against routine practice of these interventions.
It is possible that the infant born through meconium-stained fluid will require intubation for resuscitation. Therefore, trained personnel and equipment for intubation should be readily available for births where meconium- stained amniotic fluid is present.
If meconium is obstructing the trachea, suctioning by using an endotracheal tube with a meconium aspirator may be effective in relieving the obstruction

- **Heart Rate Monitoring During Neonatal Resuscitation**
  - Treatment Recommendation: not changed from 2015
  - In babies requiring resuscitation, we suggest the ECG can be used to provide a rapid and accurate estimation of heart rate (weak recommendation, very low-certainty evidence).

- **Sustained Inflation: Treatment Recommendations**
  - For preterm newborn infants who receive PPV for bradycardia or ineffective respirations at birth, we suggest against the routine use of initial sustained inflation(s) greater than 5 seconds (weak recommendation, low-certainty evidence). A sustained inflation may be considered in research settings
  - For term or late preterm infants who receive PPV for bradycardia or ineffective respirations at birth, it is not possible to recommend any specific duration for initial inflations due to the very low confidence in effect estimates.

PEEP Versus No PEEP: This treatment recommendation has not changed from 2015.

We suggest using PEEP for the initial ventilation of premature newborn infants during delivery room resuscitation (weak recommen-dation, low-quality evidence). We cannot make any recommendation for term infants because of insufficient data.

CPAP Versus Intermittent Positive Pressure Ventilation: This treatment recommendation is unchanged from 2010.

For spontaneously breathing preterm newborn infants with respiratory distress requiring respiratory support in the delivery room, we suggest initial use of CPAP rather than intubation and intermittent PPV (weak recommendation, moderate certainly of evidence).

- T-Piece Resuscitator Versus Self-Inflating Bag for Ventilation:
  - Treatment Recommendation This treatment recommendation is unchanged from 2010.
  - There is insufficient evidence regarding the use of T-piece resuscitator or self-inflating bag for initial PPV at birth, so the recommendation of one device over another would be purely speculative because the confidence in effect estimates is so low.
- Oxygen for Preterm Resuscitation: Treatment recommendation is unchanged from 2019.
  - For preterm newborn infants (less than 35 weeks' gestation) who receive respiratory support at birth, we suggest starting with a lower oxygen concentration (21% to 30%) rather than higher initial oxygen concentration (60% to 100%) (weak recommendation, very low-certainty evidence). We suggest the range of 21% to 30% oxygen because all trials used this for the low oxygen concentration group. Subsequent titration of oxygen concentration using pulse oximetry is advised (weak recommendation, very low-certainty evidence).
- **Oxygen for Term Resuscitation: Treatment recommendation is unchanged from 2019.**
  - For newborn infants at 35 weeks' or greater gestation receiving respiratory support at birth, we suggest starting with 21% oxygen (air) (weak recommendation, low certainty of evidence). We recommend against starting with 100% oxygen (strong recommendation, low certainty of evidence).

CPR Ratios for Neonatal Resuscitation: Treatment recommendation is unchanged from 2015.
We suggest continued use of a 3:1 compression-to-ventilation ratio for neonatal CPR (weak recommendation, very low-quality evidence).

Thumb Versus 2-Finger Compressions for Neonatal Resuscitation: Recommendation is unchanged from 2015.
We suggest that chest compressions in the newborn infant should be delivered by the 2-thumb, hands-encircling-the-chest method as the preferred option (weak recommendation, very low-certainty evidence).

Epinephrine (Adrenaline) for Neonatal Resuscitation: Recommendations
If the heart rate has not increased to 60/min or greater after optimizing ventilation and chest compressions, we suggest the administration of intravascular epinephrine (adrenaline) (0.010.03 mg/kg) (weak recommendation, very low-certainty evidence).
If intravascular access is not yet available, we suggest administering endotracheal epinephrine (adrenaline) at a larger dose (0.05 0.1 mg/kg) than the dose used for IV administration (weak recommendation, very low-certainty evidence).
The administration of endotracheal epinephrine (adrenaline) should not delay attempts to establish vascular access (weak recommendation, very low-certainty evidence).
We suggest the administration of further doses of epinephrine (adrenaline) every 3 to 5 minutes, preferably intravascularly, if the heart rate remains less than 60/min (weak recommendation, very low-certainty evidence).
If the response to endotracheal epinephrine (adrenaline) is inadequate, we suggest that an intravascular dose be given as soon as vascular access is obtained, regardless of the interval after any initial endotracheal dose (weak recommendation, very low-certainty evidence).

- **Intraosseous Versus Umbilical Vein for Emergency Access :**
  - We suggest umbilical venous catheterization as the primary method of vascular access during newborn infant resuscitation in the delivery room. If umbilical venous access is not feasible, the intraosseous route is a reasonable alternative for vascular access during newborn resuscitation (weak recommendation, very low- certainty evidence). Outside the delivery room setting, we suggest that either umbilical venous access or the IO route may be used to administer fluids and medications during newborn resuscitation (weak recommendation, very low-certainty evidence). The actual route used may depend on local availability of equipment, training, and experience.

- **Volume Infusion During Neonatal Resuscitation:** Treatment Recommendation are unchanged from 2010.
  - Early volume replacement with crystalloid or red cells is indicated for newborn infants with blood loss who are not responding to resuscitation. There is insufficient evidence to support the routine use of volume administration in the newborn infant with no blood loss who is refractory to ventilation, chest compressions, and epinephrine. Because blood loss may be occult, a trial of volume administration may be considered in newborn infants who do not respond to resuscitation.

- **Sodium Bicarbonate During Neonatal Resuscitation: Treatment recommendation is unchanged from 2010.**
  - Sodium bicarbonate is discouraged during brief CPR but may be useful during prolonged arrests after adequate ventilation is established and there is no response to other therapies.

- **Impact of Duration of Intensive Resuscitation:**
  - Failure to achieve return of spontaneous circulation in newborn infants despite 10 to 20 minutes of intensive resuscitation is associated with a high risk of mortality and a high risk of moderate-to-severe neurodevelopmental impairment among survivors. However, there is no evidence that any specific duration of resuscitation consistently predicts mortality or moderate-to-severe neurodevelopmental impairment. If, despite provision of all the recommended steps of resuscitation and excluding reversible causes, a newborn infant requires ongoing cardiopulmonary resuscitation (CPR) after birth, we suggest discussion of discontinuing resuscitative efforts with the clinical team and family. A reasonable time frame to consider this change in goals of care is around 20 minutes after birth. (Weak recommendation, very low-certainty evidence).

- **Rewarming of Hypothermic Newborns: Treatment Recommendation is unchanged from 2015.**
  - The confidence in effect estimates is so low that a recommendation for either rapid rewarming (0.5 C/h or greater) or slow rewarming (0.5 C/h or less) of unintentionally hypothermic newborn infants (temperature less than 36 C) at hospital admission would be speculative.

- **Induced Hypothermia in Settings With Limited Resources**: recommendation is unchanged from 2015.
- We suggest that newborn infants at term or near-term with evolving moderate-to-severe hypoxic-ischaemic encephalopathy in low-in-come countries and/or other settings with limited resources may be treated with therapeutic hypothermia (weak recommendation, low-quality evidence). Cooling should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, anticonvulsants, and pathology testing. Treat-ment should be consistent with the protocols used in the randomized clinical trials in developed countries, ie, cooling to commence within 6 hours, strict temperature control at 33 C to 34 C for 72 hours and rewarming over at least 4 hours.

- **Postresuscitation Glucose Management:** Treatment recommendation is unchanged from 2010.
  - Intravenous glucose infusion should be considered as soon as practical after resuscitation, with the goal of avoiding hypoglycemia

- **Topics Not Reviewed in 2020 :**
  - Term umbilical cord management
  - Preterm umbilical cord management
  - Babies born to mothers who are hypothermic or hyperthermic
  - Stimulation for apneic newborns
  - Respiratory function monitoring in the delivery room