Neuroprotection in the NICU: Current and Future

2021 대한재활의학회 추계학술대회

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정의석

ASAN Medical Center Children's Hospital

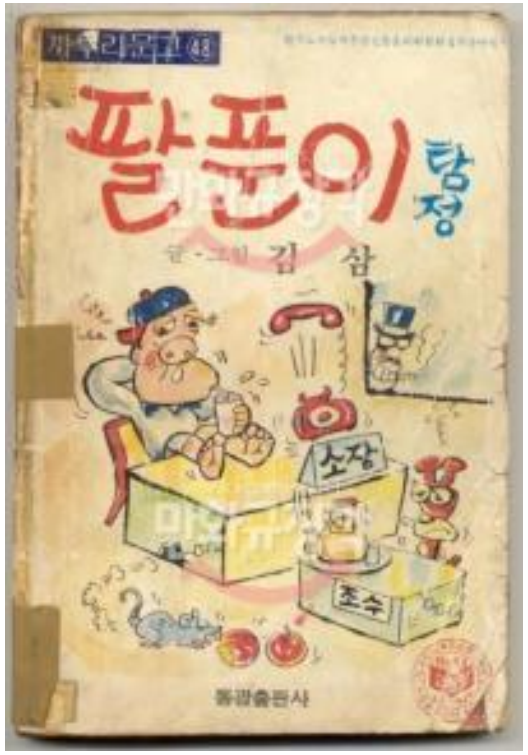
Contents

미숙아 (未熟兒, preterm infant)

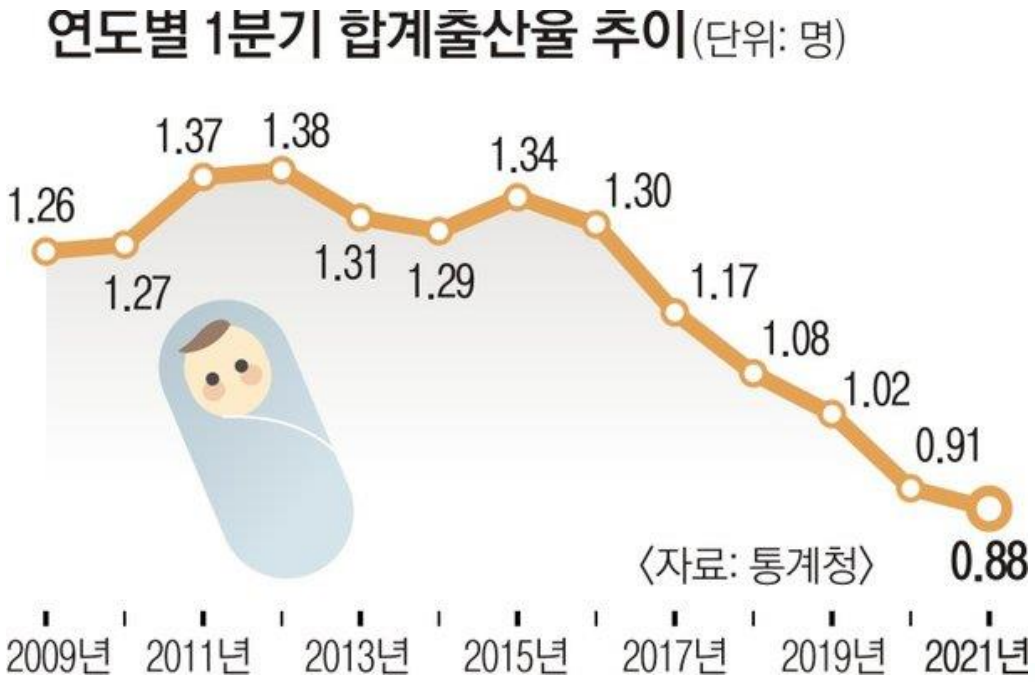
- ✓ 세계보건기구(WHO)에 의하면 재태 기간 37주 미만 또는 최종 월경 일로부터 259일 미만에 태어난 아기를 미숙아(preterm infant) 또는 조산아라고 한다.

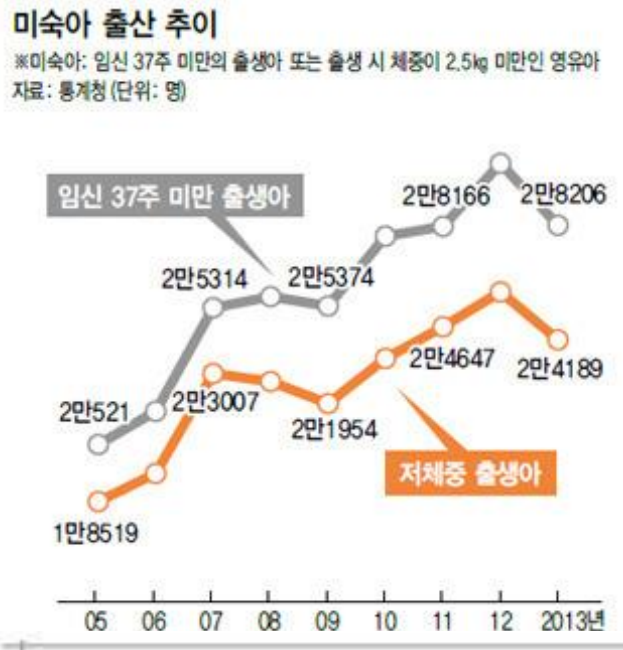
- ✓ 이른둥이 (순우리말)

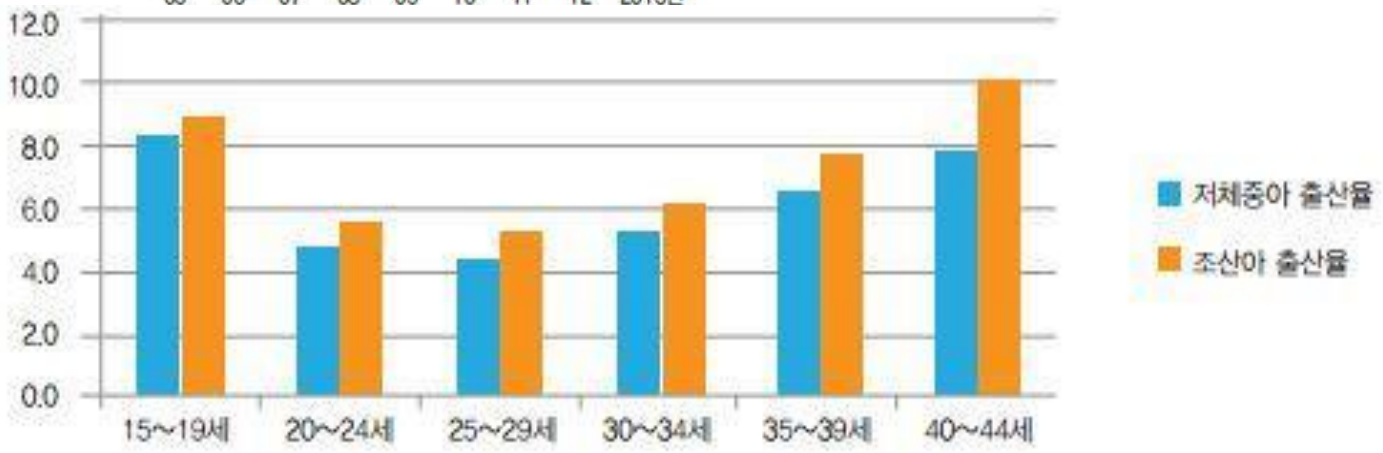
- ✓ 칠푼이, 팔푼이



이른둥이 (未熟兒, premature infant)





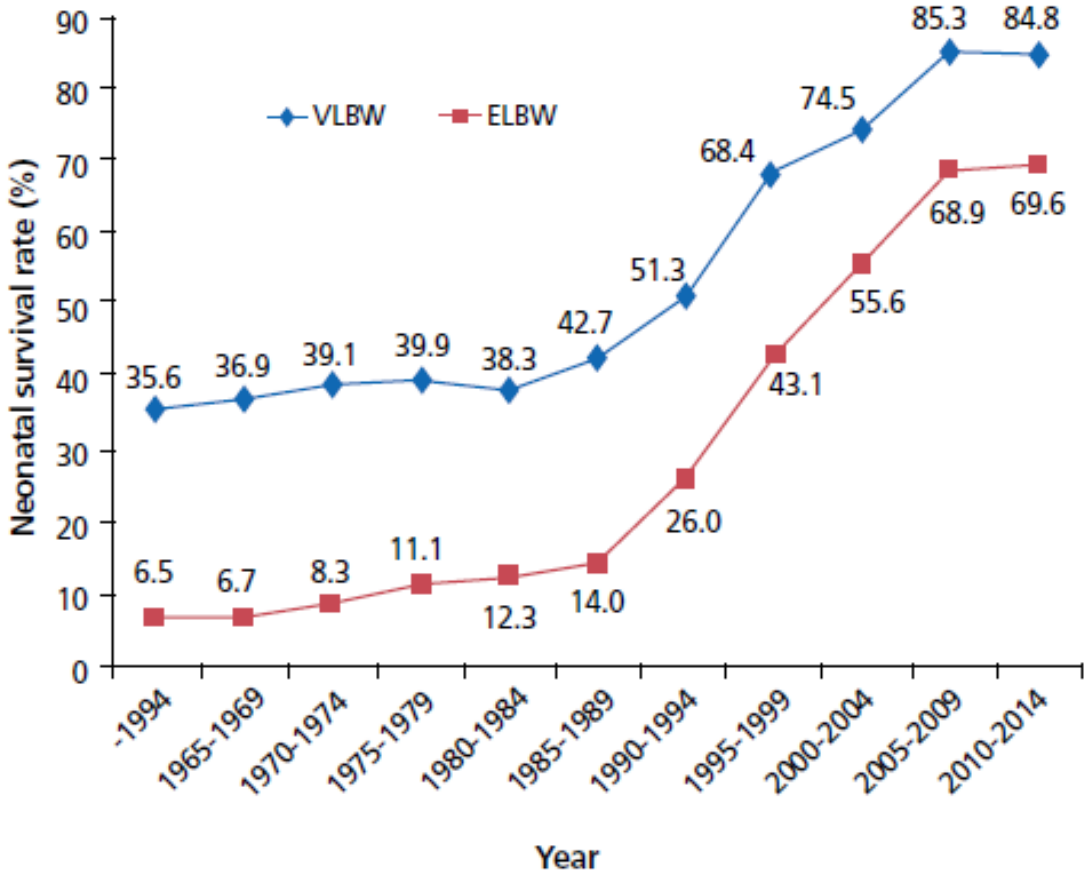


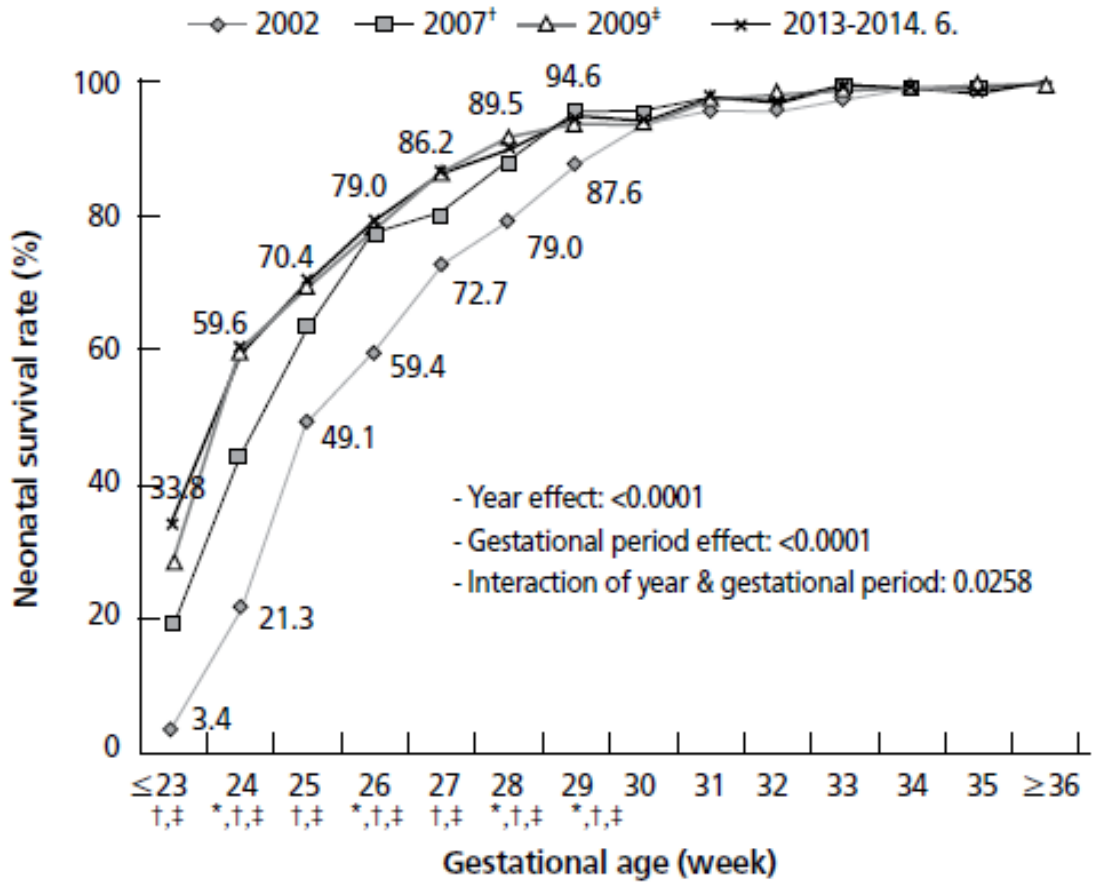
출산 연령의 고령화

인공 임신의 증가

10% 정도가 이른둥이!

Prematurity in Korea

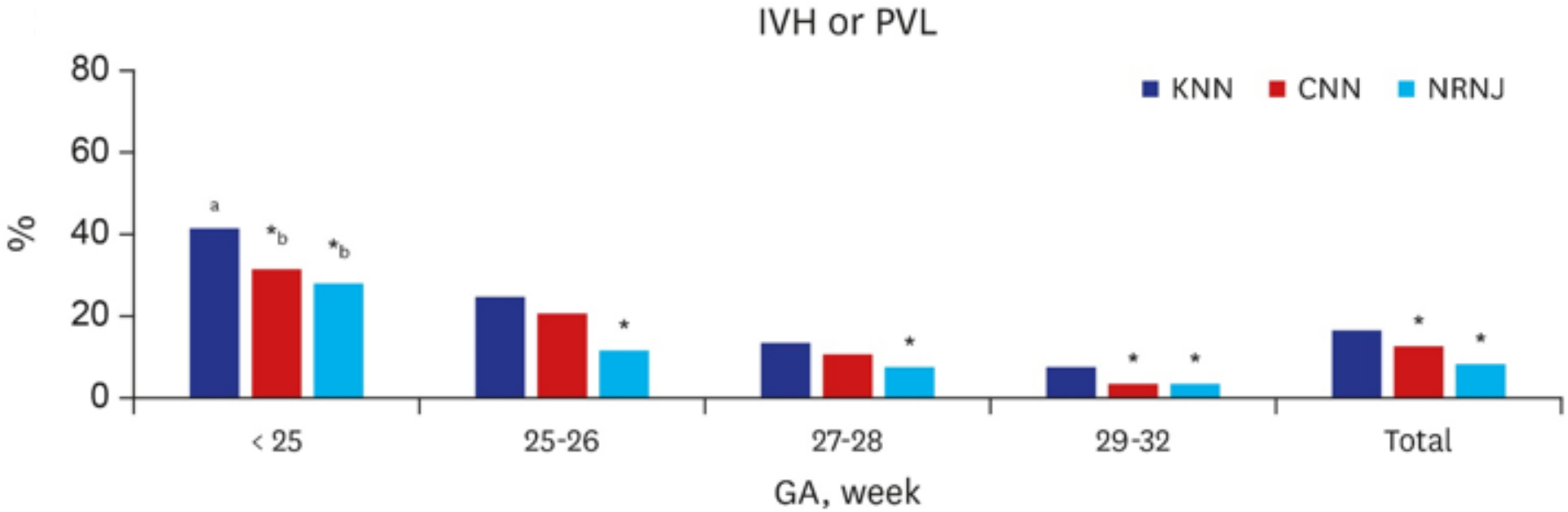




J Korean Med Assoc. 2016;59:498-505.

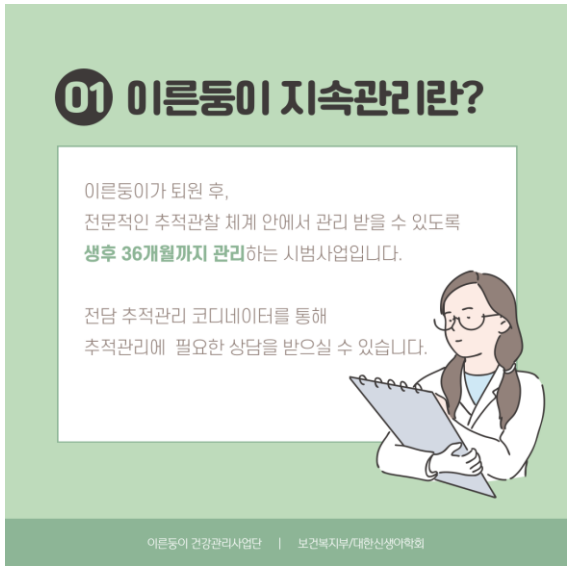
우리 아기는 잘 자랄 수 있을까요?

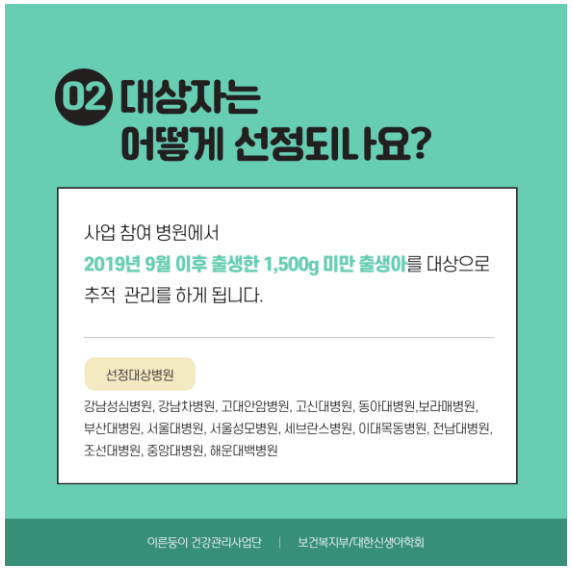
Severe neurologic injury in VLBW infants

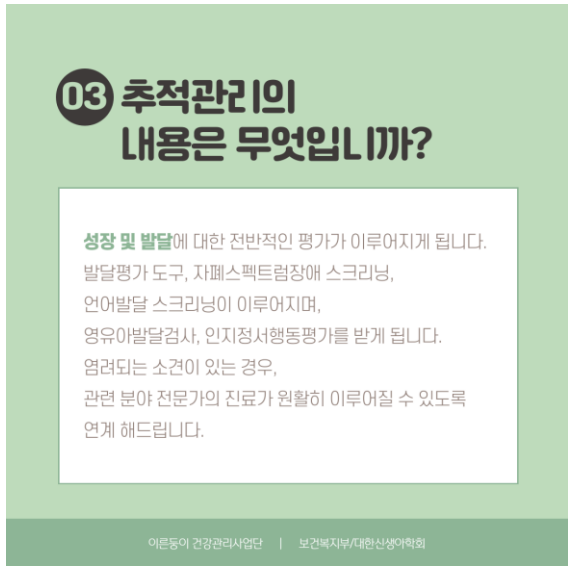


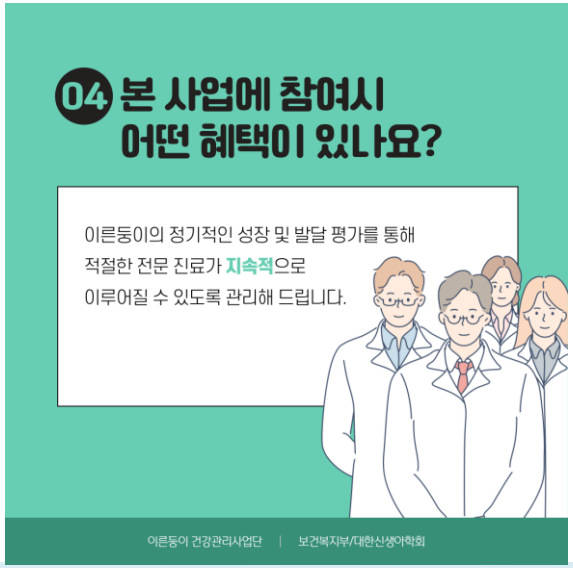
J Korean Med Sci. 2019;34(5):e40.

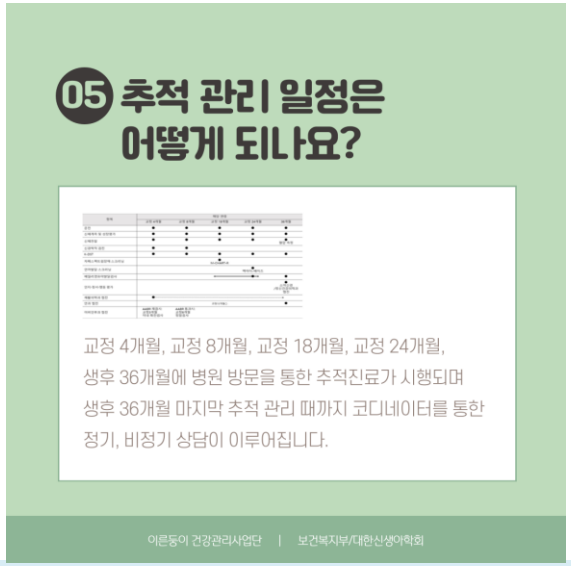
Follow-up program for preterm infants







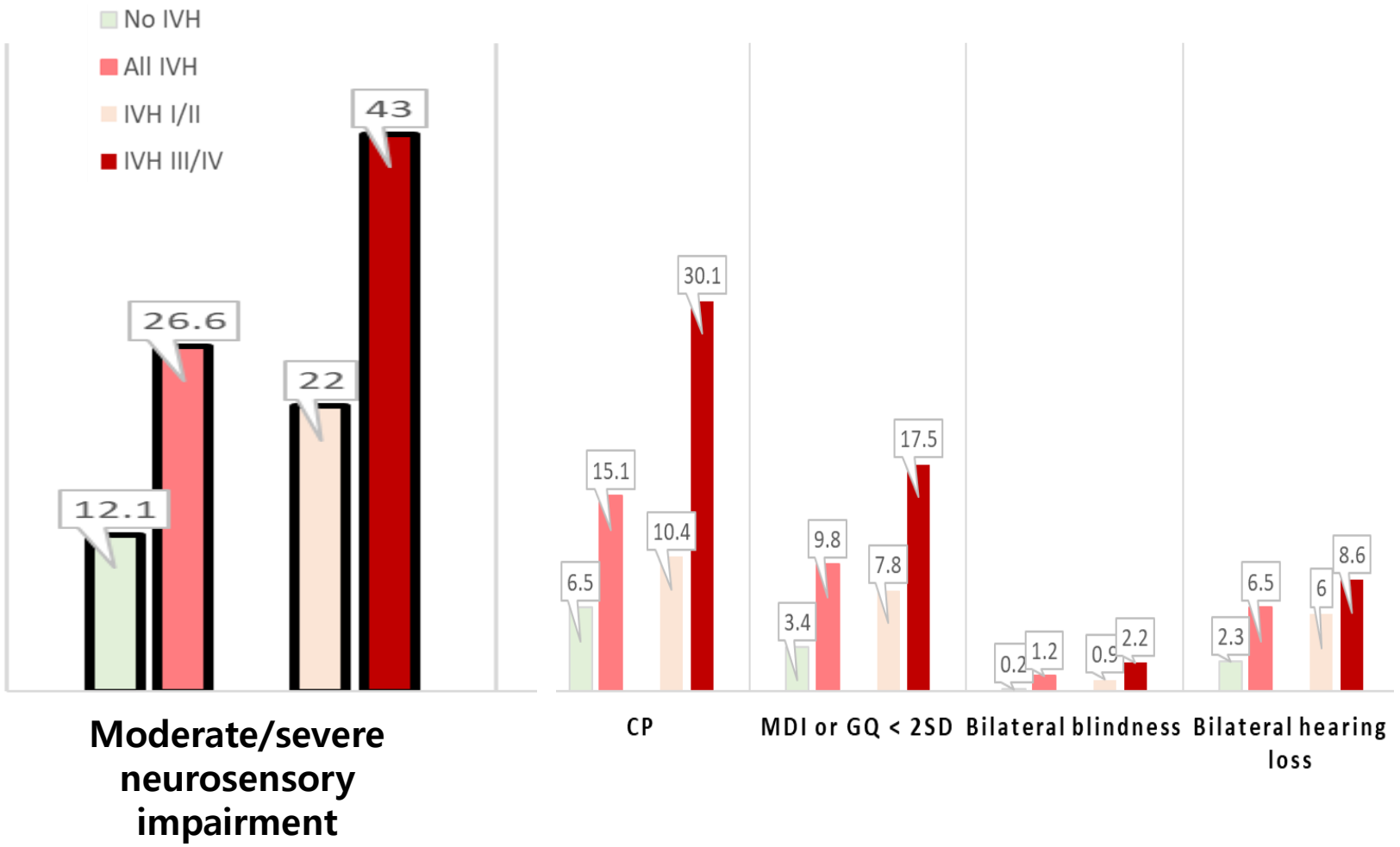




어떻게 하면
우리 아기는 잘 자랄 수 있을까요?

Contents

IVH and neurodevelopmental outcome at 2-3YO



US abnormalities and adolescent psychiatric disorders

Nondisabled survivors (exclusion: CP or IQ <55)

PL, parenchymal lesion
VE, ventricular enlargement

Psychiatric Disorders	Adjusted[a] GM/IVH	Adjusted[a] PL/VE
Current		
ADHD–inattentive type	1.01 (0.19-5.44)	6.83[c] (1.26-36.91)
Major depression	2.23 (0.80-6.24)	No cases[d]
Tic disorders	1.89 (0.42-8.57)	9.77[c] (1.69-56.47)
Obsessive-compulsive disorder	11.85[b] (3.22-43.62)	15.32[c] (1.82-128.74)
Lifetime		
ADHD–inattentive type	0.64 (0.24-1.74)	1.13 (0.31-4.10)
Major depression	2.59[c] (1.02-6.58)	No cases[d]
Tic disorders	0.85 (0.21-3.51)	5.02[c] (1.05-23.92)
Obsessive-compulsive disorder	11.85[b] (3.22-43.62)	15.32[c] (1.82-128.74)

Adjusted for maternal social risk at birth, sex, completed weeks of gestation, fetal growth ratio, multiple birth, maternal smoking, maternal drinking, active labor, birth presentation, base excess from the first postnatal blood gas, thyroid status, hypocapnia, hyperoxia, systolic hypotension, and prolonged ventilation.

Whitaker, Arch Gen Psychiatry 2011

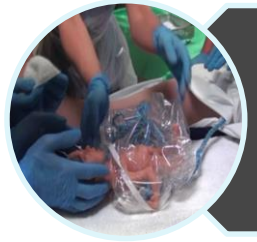
Prevention of GMH/IVH

Delivery plan

- Prevention of preterm birth

Prenatal pharmacologic interventions

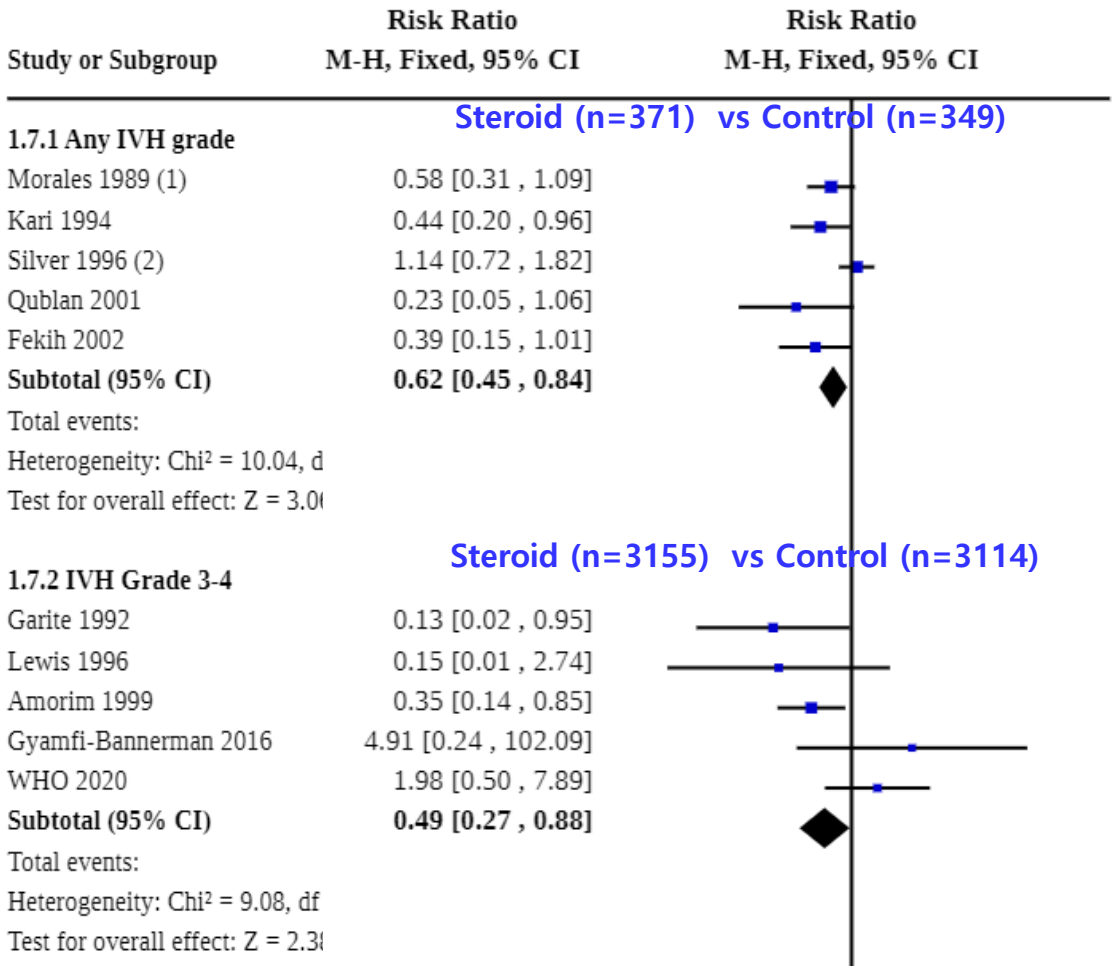
- Corticosteroid



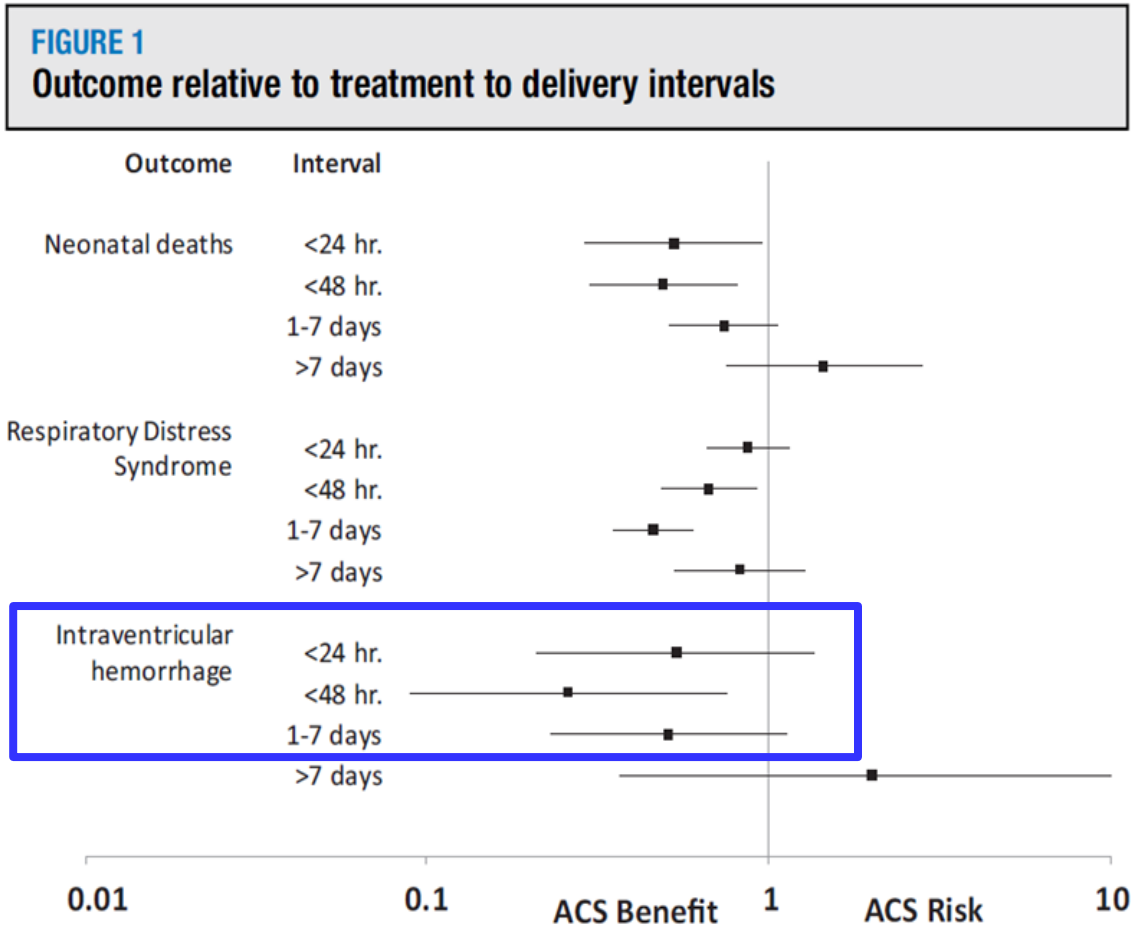
DR management

- Resuscitation

Antenatal corticosteroid (ANS)

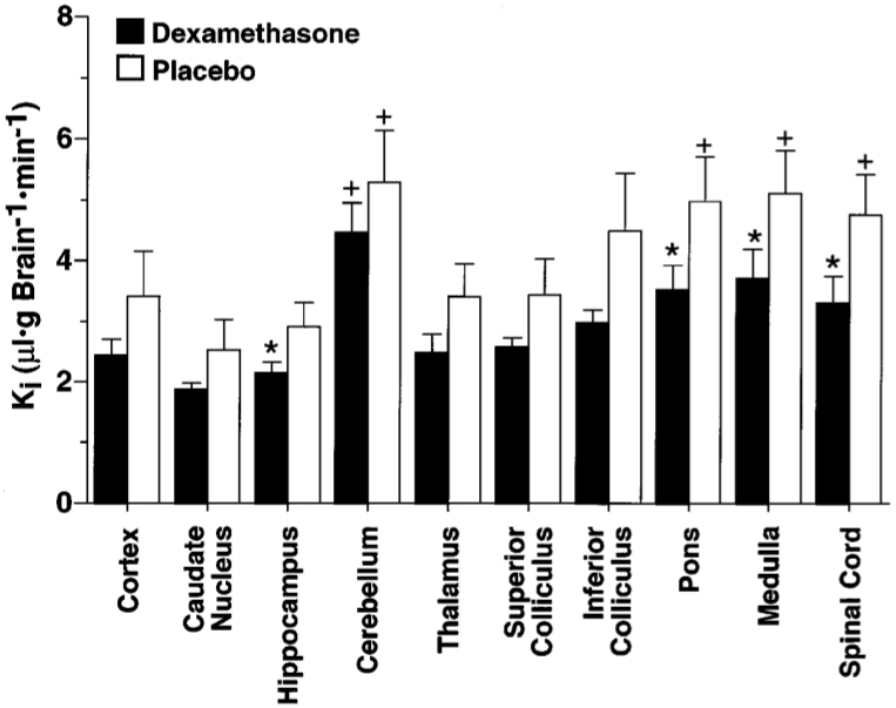


McGoldbrick, Cochrane Reviews 2020



Jobe, Am J Obstet Gynecol 2018

ANS stabilizes GM vasculature



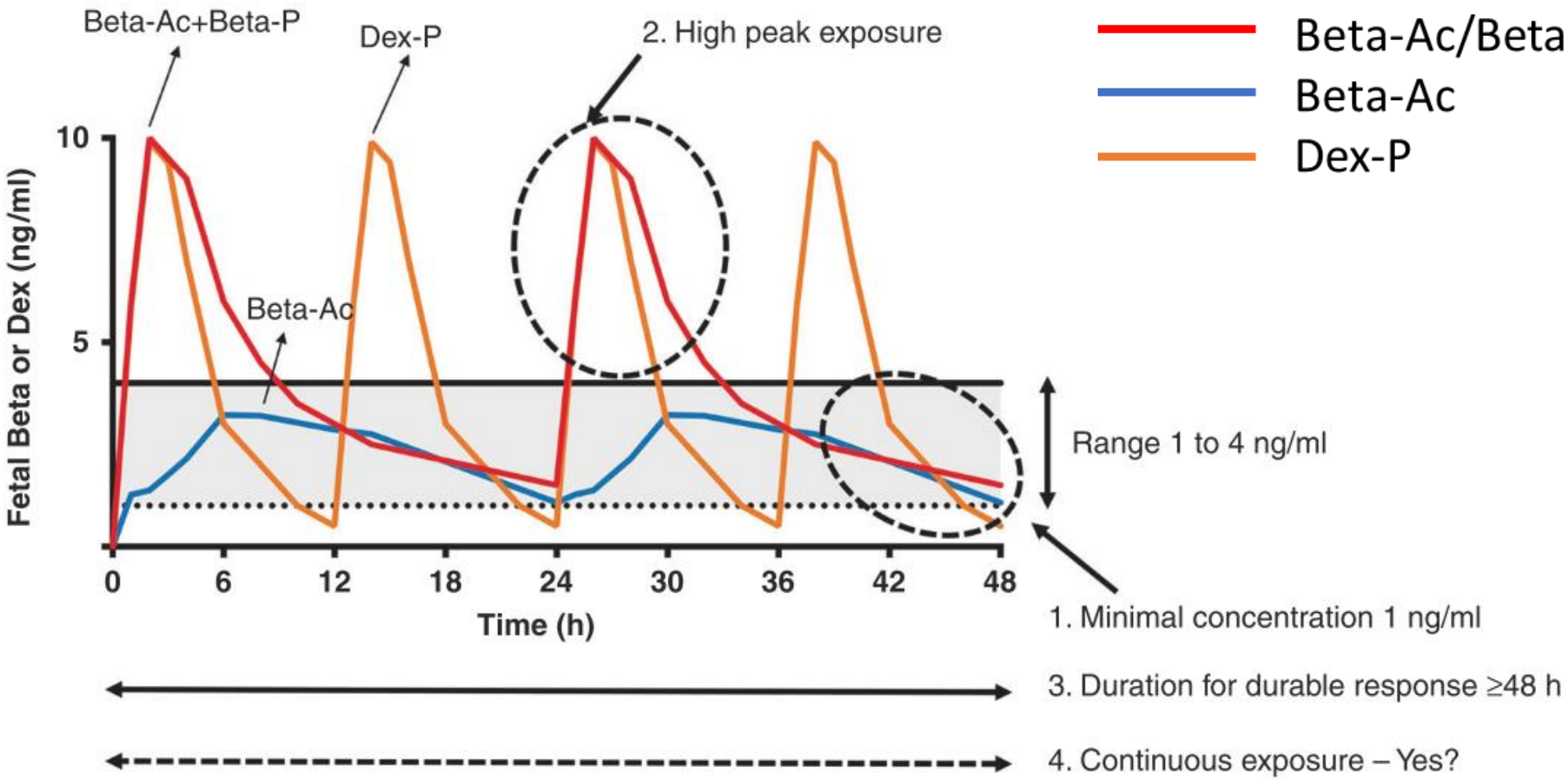
- Pregnant ewe, 120 days of gestation
- Dexamethasone 6 mg x 4 doses
- Blood-to-brain transfer constant (Ki) for α-aminoisobutyric acid

Stonestreet, Am J Physiol 1999

- ↓VEGF
- ↑ coverage of nascent endothelial cells with pericytes and astrocyte foot processes
- ↑ basal lamina fibronectin
- Inhibition of neurovascular proteases
- ↑ vascular tone and BP stability

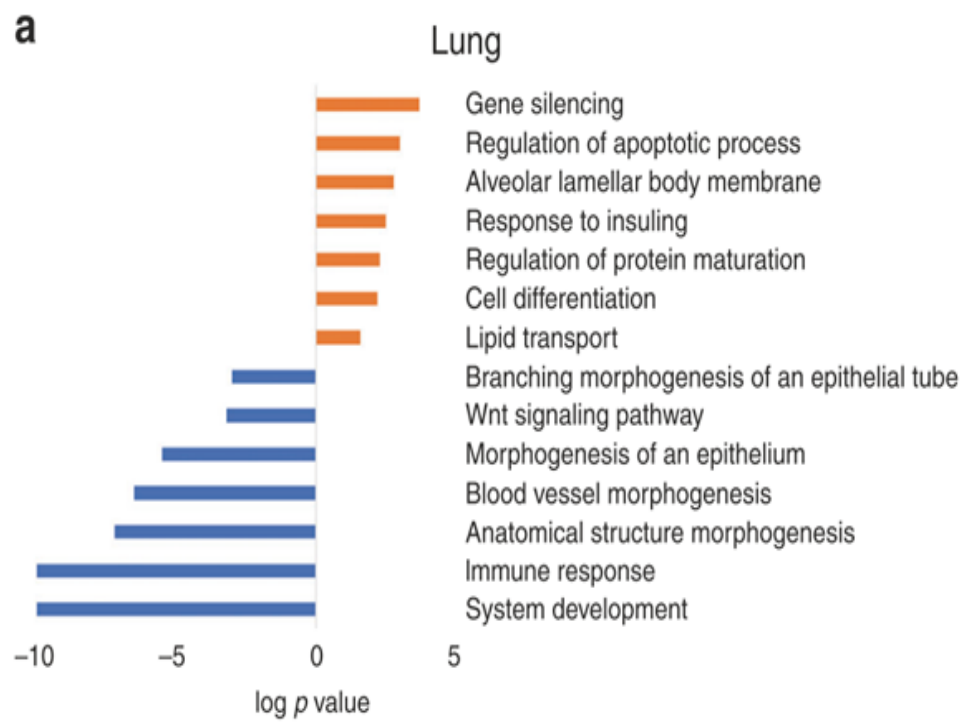
Liebowitz, J Pediatr 2016

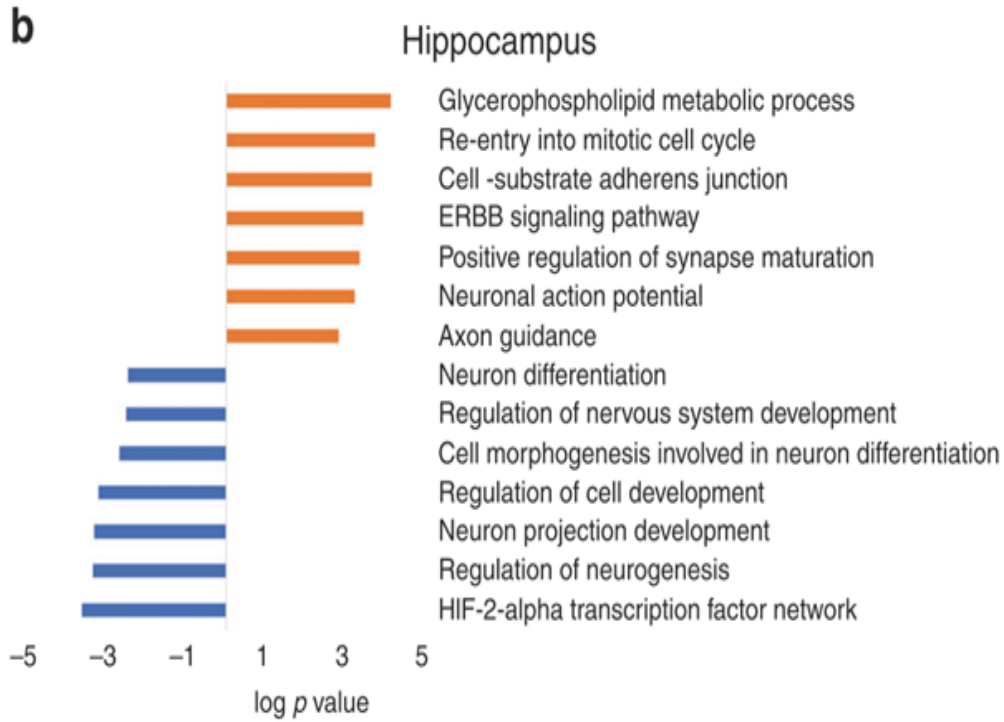
Unanswered questions about ANS strategies



Jobe, Pediatr Res 2021

Unanswered questions about ANS strategies





↑ Surfactant production
↑ Lung compliance

↓ Morphogenesis of epithelium and vessels

↑ Synaptic maturation

↓ Neuronal differentiation
↓ Neuron development

Jobe, Pediatr Res 2021

Antenatal MgSO4

Trial	N	GW	MgSO4 dose	Death	Cerebral palsy	Composite outcome	Other outcomes
ACTOMgSO4 (JAMA 2003)	1062	< 30	4 g -> 1 g/h for max 24h	• 13.8 vs 17.1% RR 0.83 (95% CI 0.64-1.09)	• 6.8 vs 8.2% RR 0.83 (0.54-1.27)	•Death or CP :19.8 vs 24.0% RR 0.83 (0.66-1.03)	•Substantial gross mot or dysfunction:3.4 vs 6. 6% RR 0.51 (0.29-0.91) • Death or substantial gross motor dysfunctio n :17.0 versus 22.7% RR 0.75 (0.59-0.96)
BEAM (NEJM 2008)	2241	24 to 31	6 g -> 2 g/h for max 12h	• 9.5 vs 8.5% RR 1.12 (0.85-1.47)	• mod/severe CP :1.9 vs 3.5% RR 0.55 (0.32-0.95*)	• Stillbirth or infant death by 1YO or mod/severe C P at or beyond 2YO of C A	
PREMAG (BJOG 2007; Gynecol Obstet Fertil 2008)	573	< 33	4 g loading no maintenan-ce dose			n or death :OR 0.62 (0.41-0.93)	

- Stabilizing BP and normalizing cerebral blood flow.
- Blockade of excitatory neurotransmitters, such as glutamate.
- Antioxidant effects.
- Anti-inflammatory effects.

Summary from www.uptodate.com 2021

Umbilical cord care at delivery room

- P: GA < 30 weeks
- IC: immediate CC (n=782) vs delayed CC (n=784)
- O: no difference in major outcomes

✓ death or major morbidities (37.2% vs 37.0%)

✓ death or severe brain injury (15.3 vs 13.6%)

✓ IVH grade 3/4 (2.4 vs 3.4%),

Tannow-Mordi, NEJM 2017

Umbilical cord care at delivery room

Severe IVH	UCM	DCC	P-value
Overall	20/236 (8)	9/238 (3)	0.02
23-27 wks	**20/93 (22)**	**5/89 (6)**	**0.002**
28-31 wks	0/143 (0)	3/149 (2)	0.24
C/S	10/180 (6)	6/159 (4)	0.44
V/D	10/56 (18)	2/79 (3)	0.004

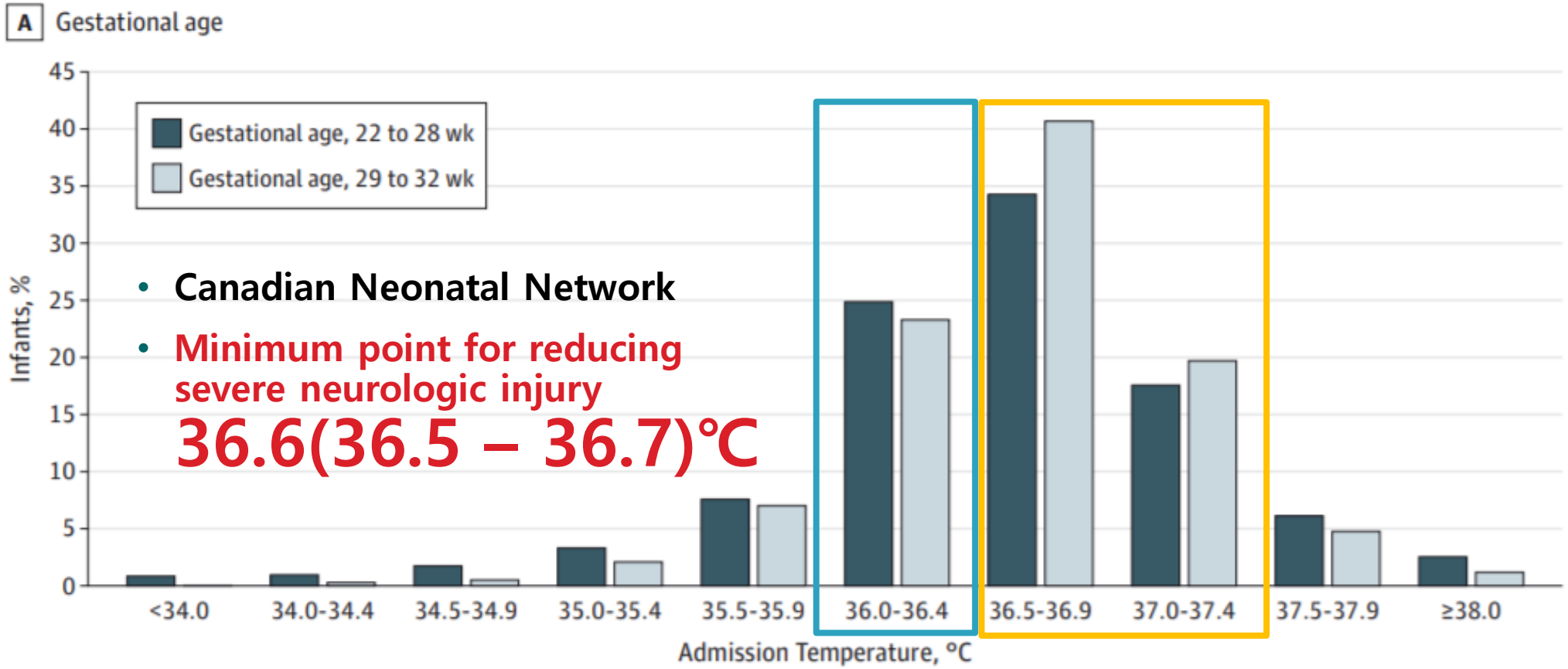
- P: GA 23-32 weeks
- I: umbilical cord milking (n=236)
- C: delayed CC (n=238)
- O: prematurely terminated after first interim analysis

✓ death or severe IVH (12% vs 8%, P=0.16)

Katheria, JAMA 2019

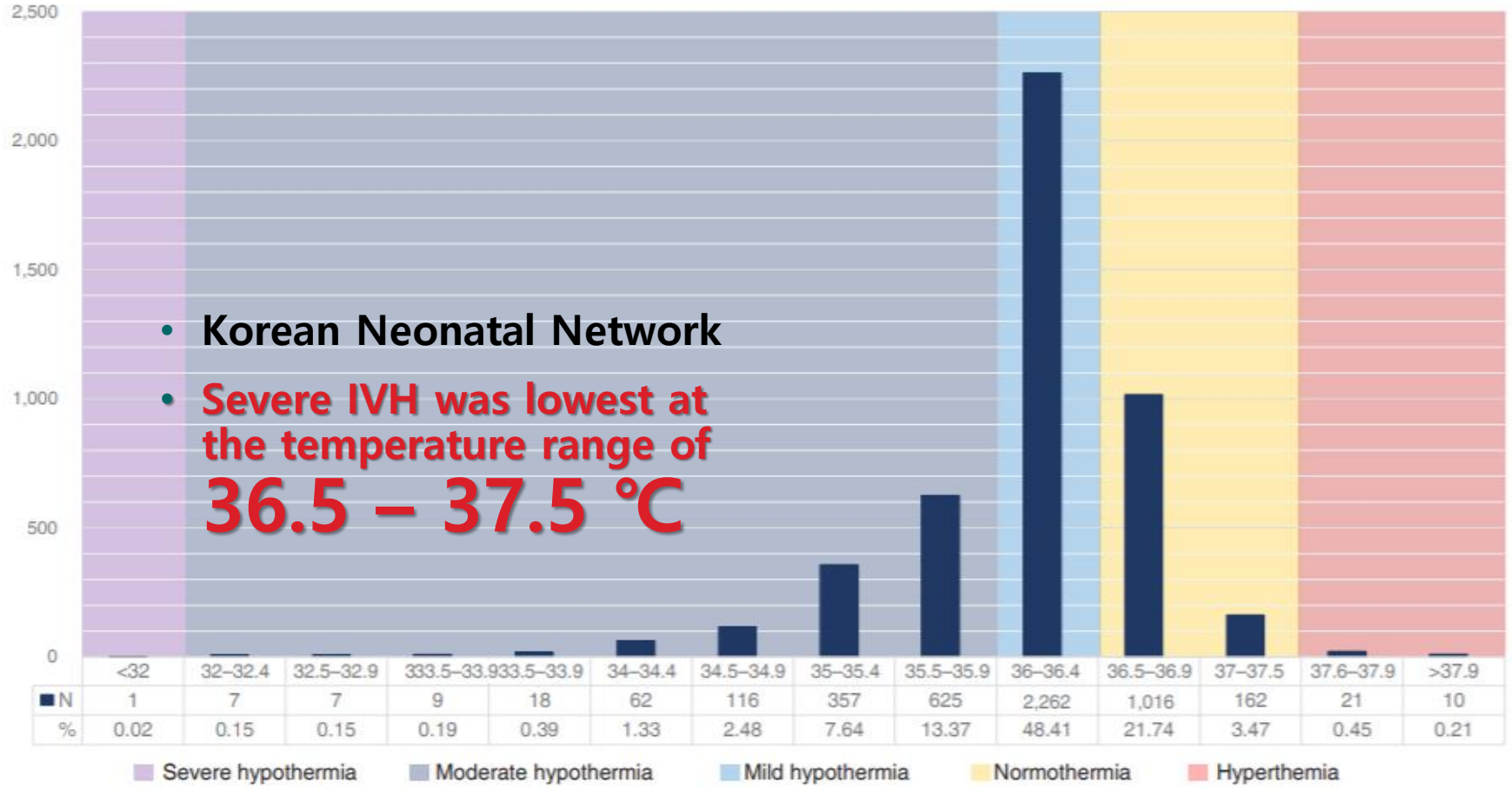
Temperature at admission

Figure 1. Temperature Distribution According to Gestational Age and Birth Weight



Lyu, JAMA Pediatr 2015

Temperature at admission



	<32	32–32.4	32.5–32.9	333.5–33.9	33.5–33.9	34–34.4	34.5–34.9	35–35.4	35.5–35.9	36–36.4	36.5–36.9	37–37.5	37.6–37.9	>37.9
N	1	7	7	9	18	62	116	357	625	2,262	1,016	162	21	10
%	0.02	0.15	0.15	0.19	0.39	1.33	2.48	7.64	13.37	48.41	21.74	3.47	0.45	0.21

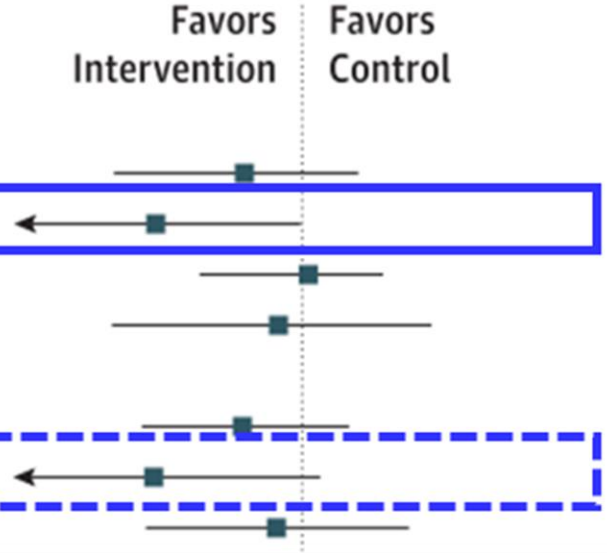
Fig. 1. Admission temperature distribution. Only 25.2% of infants had a normal admission temperatures ranging from 36.5°C to 37.5°C. Approximately 74.1% of infants had hypothermia <36.5°C, and 0.66% had hyperthermia >37.5°C at neonatal intensive care unit admission.

Lee, Korean J Pediatr 2019

Less invasive surfactant administration

A Severe intraventricular hemorrhage

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)
MV (control)				
INSURE	409	1	28 Fewer (33 More-68 fewer)	0.72 (0.35-1.35)
LISA	211	1	58 Fewer (1 Fewer-86 fewer)[a]	0.44 (0.19-0.99)
Nasal CPAP	2301	3	2 More (44 Fewer-50 more)	1.02 (0.57-1.55)
NPPV			13 Fewer (68 Fewer-90 more)	0.87 (0.35-2.03)
Nasal CPAP (control)				
INSURE	1390	8	23 Fewer (20 More-47 fewer)	0.71 (0.41-1.27)
LISA			46 Fewer (7 More-66 fewer)	0.43 (0.19-1.09)
NPPV	822	6	11 Fewer (47 Fewer-56 more)	0.86 (0.42-1.78)



Isayama, JAMA 2016

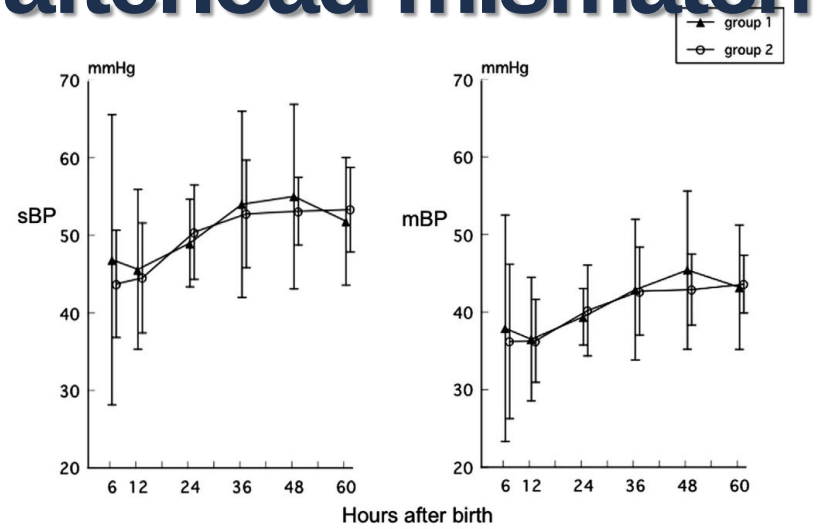
Less invasive surfactant administration

Clinical characteristics	No surfactant	LISA	Surfactant ETT	p*	Adjusted OR* (95% CI); p	Adjusted OR[1–12] (95% CI); p	all
Number of infants	1214	2624	3695				7533
Clinical sepsis	27.4	34.9	46.3	<0.001	0.76 (0.68–0.85); p<0.001	0.86 (0.74–0.99); p = 0.048[1]	39.3
Blood-culture proven sepsis	11.6	14.6	19.6	<0.001	0.87 (0.75–1.0) p = 0.053	1.0 (0.83–1.21); p = 0.9[2]	16.6
Pneumonia	2.0	4.7	8.0	<0.001	0.67 (0.54–0.84) p = 0.001	0.68 (0.51–0.81); p = 0.012[3]	5.8
Intracerebral hemorrhage grade II-IV	4.8	12.9	24.3	<0.001	0.55 (0.48–0.64); p<0.001	0.62 (0.53–0.73); p<0.001[4]	17.2
Periventricular leukomalacia	2.4	3.6	5.5	<0.001	0.72 (0.56–0.94); p = 0.015	0.75 (0.56–1.01); p = 0.06[5]	4.3

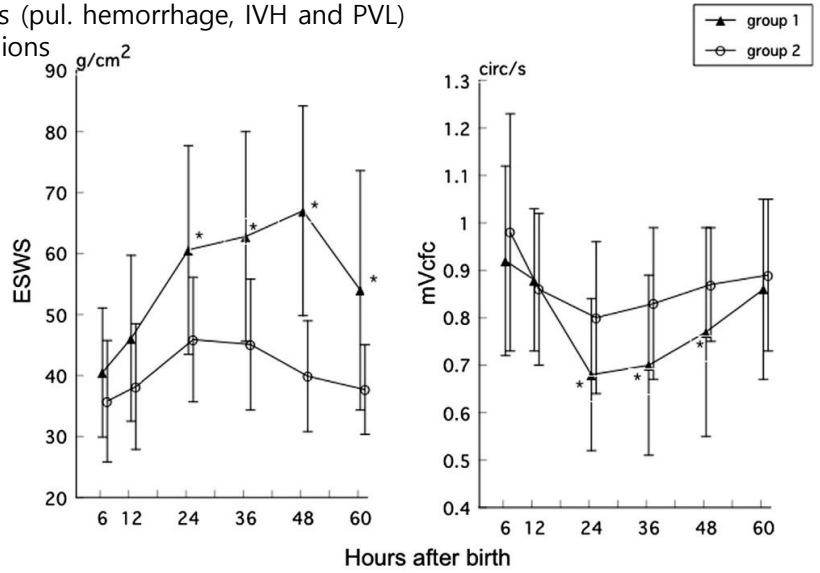
VLBWI with GA< 28+6 weeks

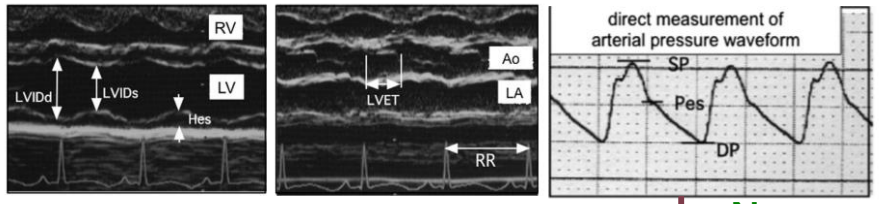
Härtel, Sci Rep 2018

Early afterload mismatch

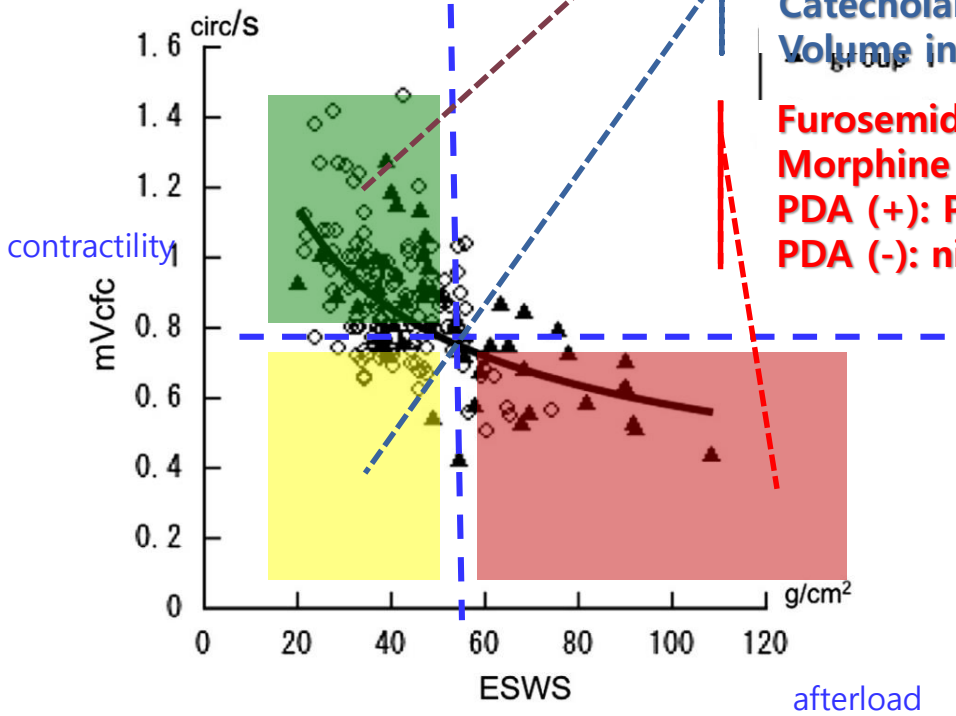


Group 1: with complications (pul. hemorrhage, IVH and PVL)
Group 2: without complications





mVcfc (circ/s) = {(LVIDd LVIDs)/LVIDd} x $RR^{1/2}$/ET;
ESWS (g/cm^2) = 1.35X LVIDs x Pes /{4XHes(1 + Hes/LVIDs)}



No pump dysfunction

Hydrocortisone
Catecholamine
Volume infusion

Furosemide
Morphine (sedation)
PDA (+): PG inhibitors
PDA (-): nitroglycerin

Toyoshima, J Formos Med Assoc 2013

Bundle for reducing severe IVH

Highest risk preterm infants prior to delivery: ≤30 weeks' gestation; may consider if birth weight ≤1500 grams and up to 32 weeks if critical (i.e. moderate-severe respiratory distress syndrome)
Golden Hour Strategy • Delayed Cord Clamping • Optimized Cardiopulmonary Resuscitation – better team communication, improved use of the T-piece resuscitator, intubation by the most experienced provider • Adequate Thermoregulation
Delivery Room Protocols: 1) Increased temperature in resuscitation room to 80°F 2) Use of plastic "body bag" during resuscitation 3) Use of exothermic warming mattress during resuscitation 4) Intubation by most experienced provider 5) Continuous monitoring of rectal temperature during resuscitation
Transport Protocols: 1) No transport if infant's temperature <36.5°C 2) Keep head midline and elevated at 30°
NICU Protocols: 1) Cluster Care and Touch Times every 6 hours for the first 72 hours 2) Head midline and elevated at 30° 3) Arterial line access to prevent heel sticks and cuffed blood pressure determination

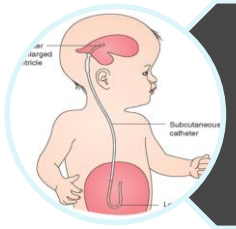
Chiriboga, J Perinatol 2019

Contents

Management of IVH – Post Hemorrhagic Hydrocephalus

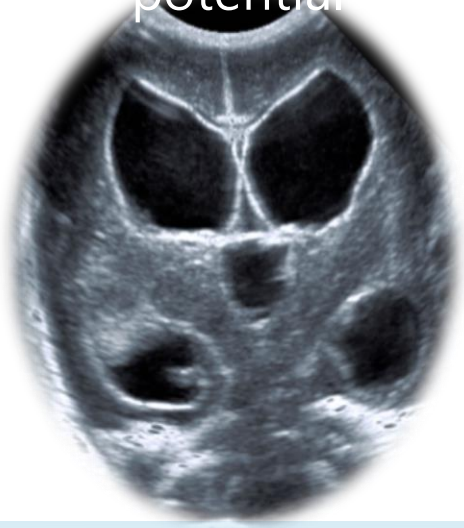
Diagnosis

- US-guided assessment

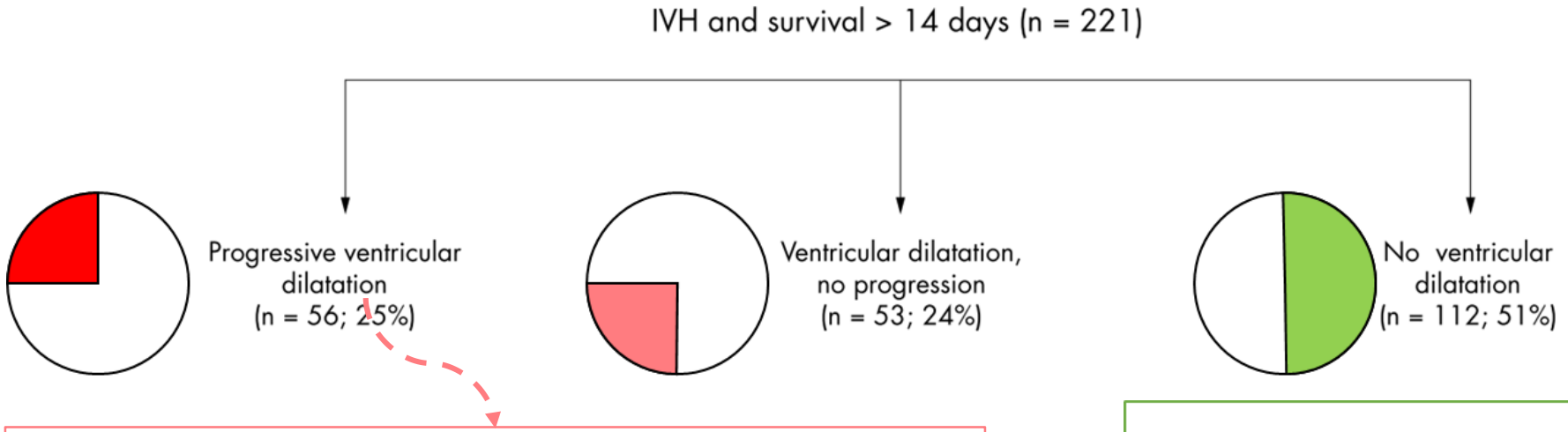


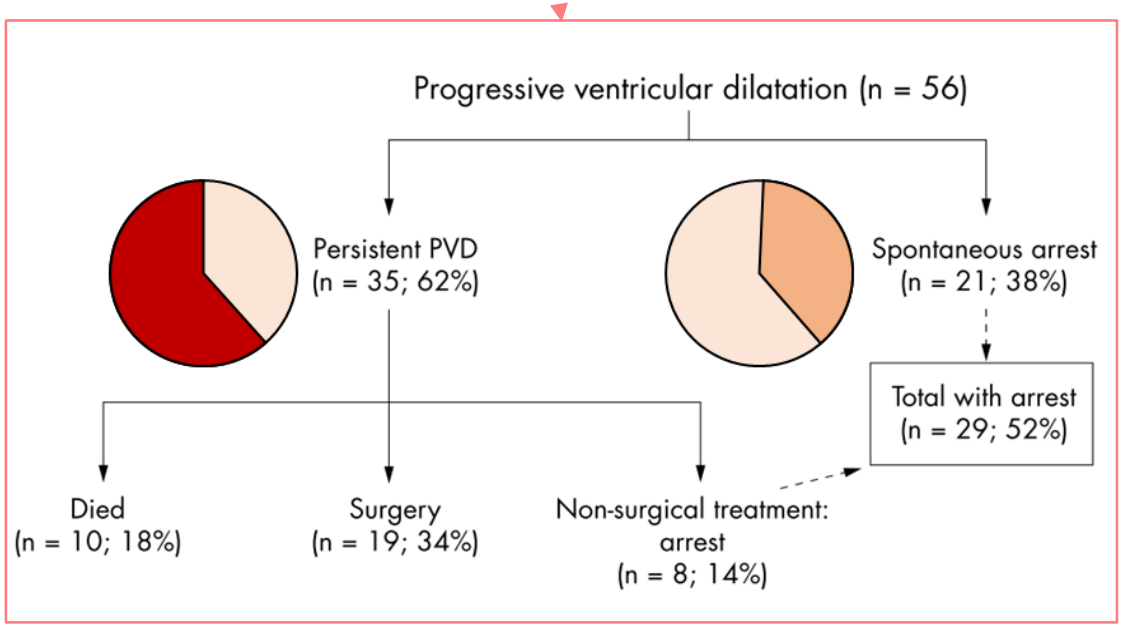
Intervention

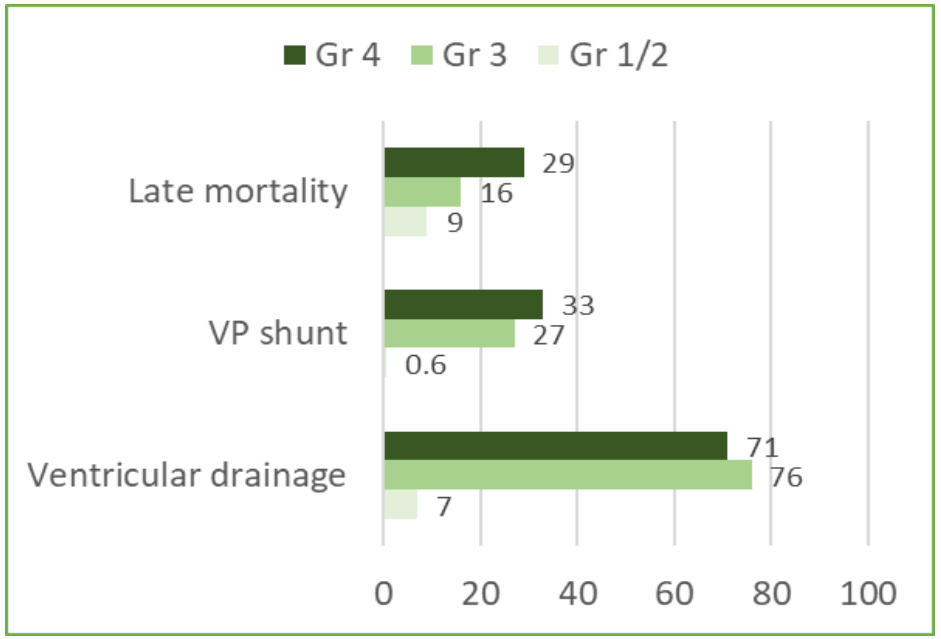
- drainage for PVHD potential



Fate of PHH in survivors

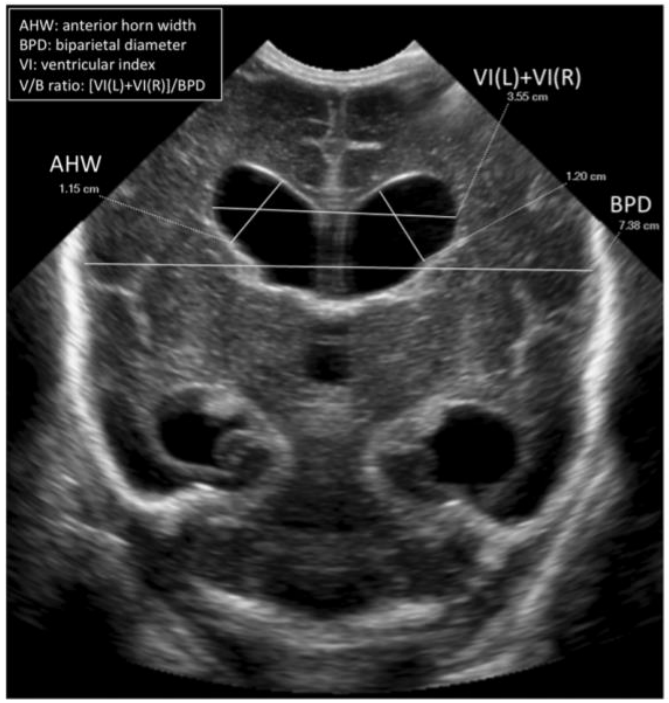


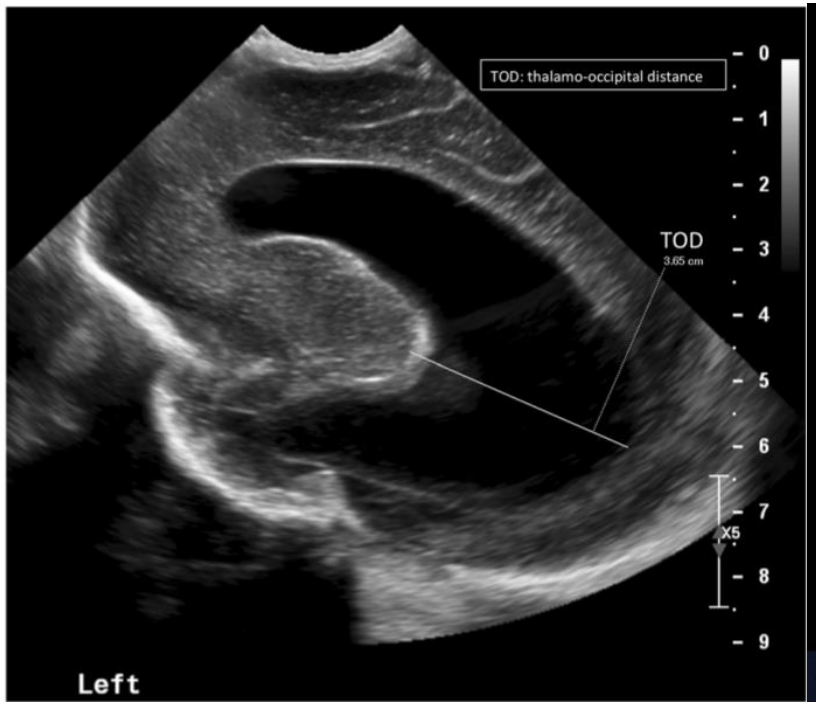


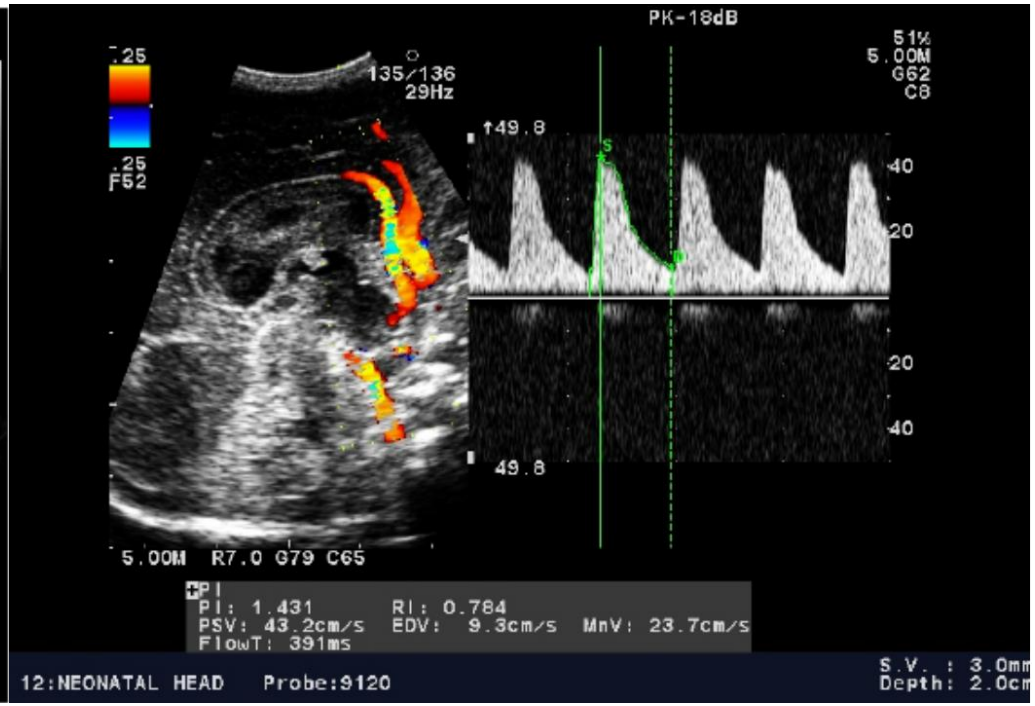


Murphy, Arch Dis Child Fetal Neonatal Ed 2002

US-guided assessment of PHH

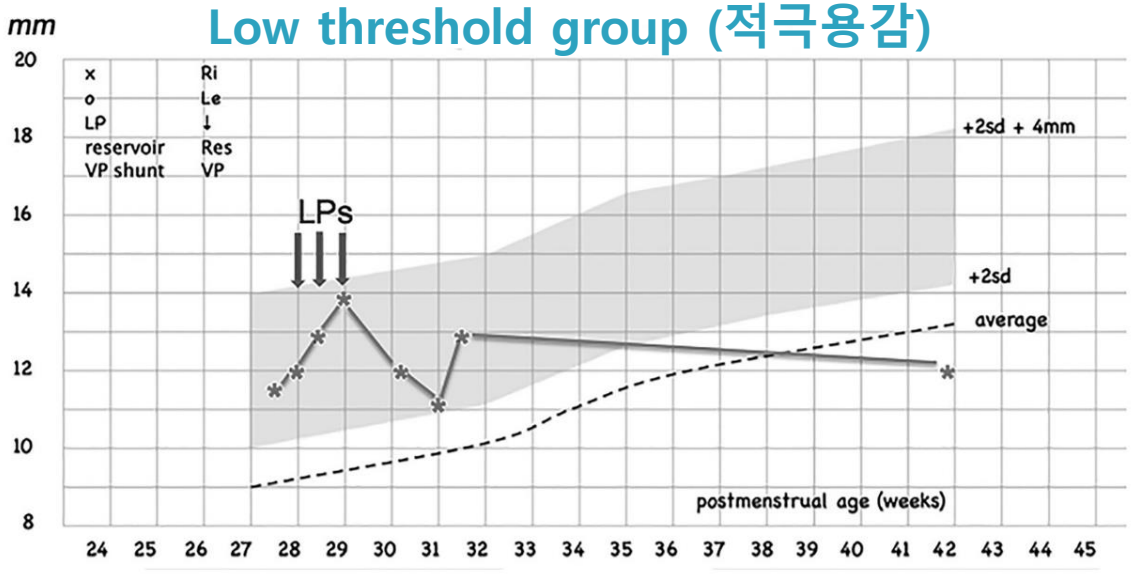


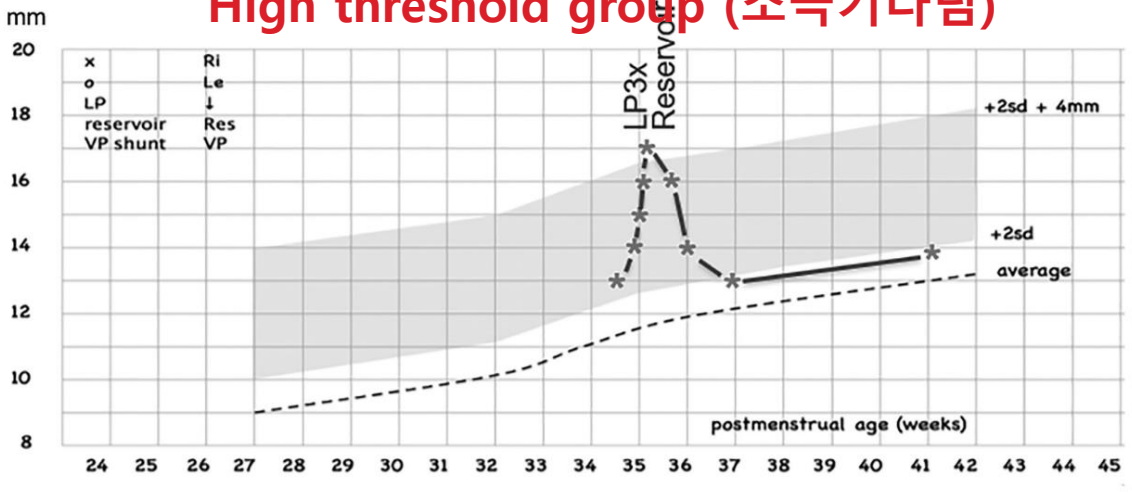


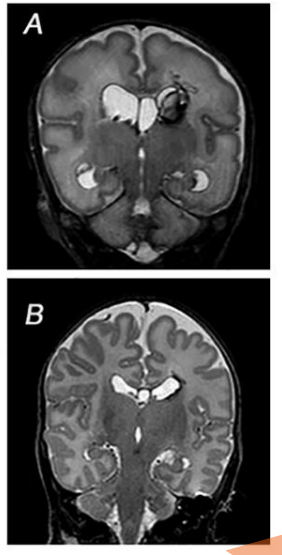


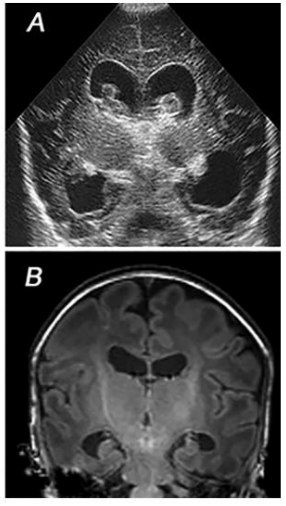
Dorner, J Perinatol 2018

ELVIS trial





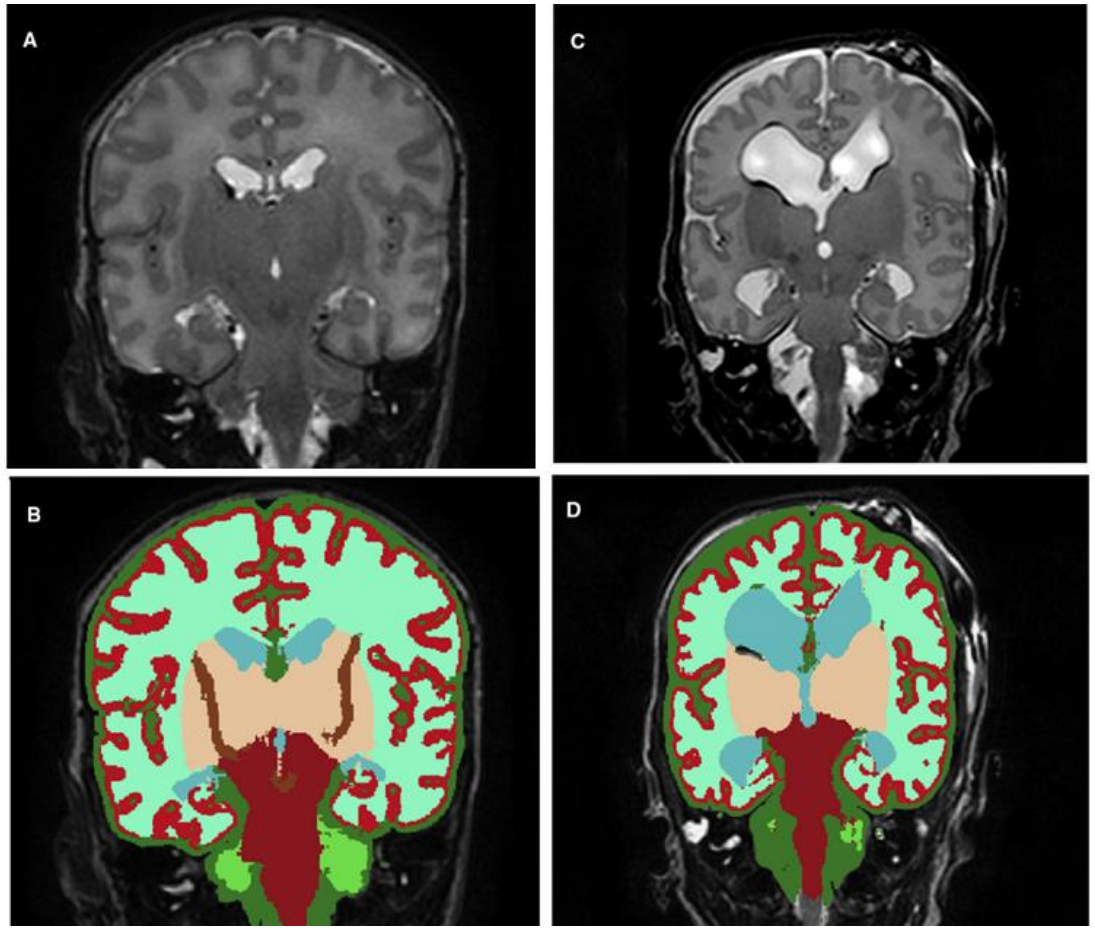




No difference in death of VP shunt

De Vries, Arch Dis Child Fetal Neonatal Ed 2019

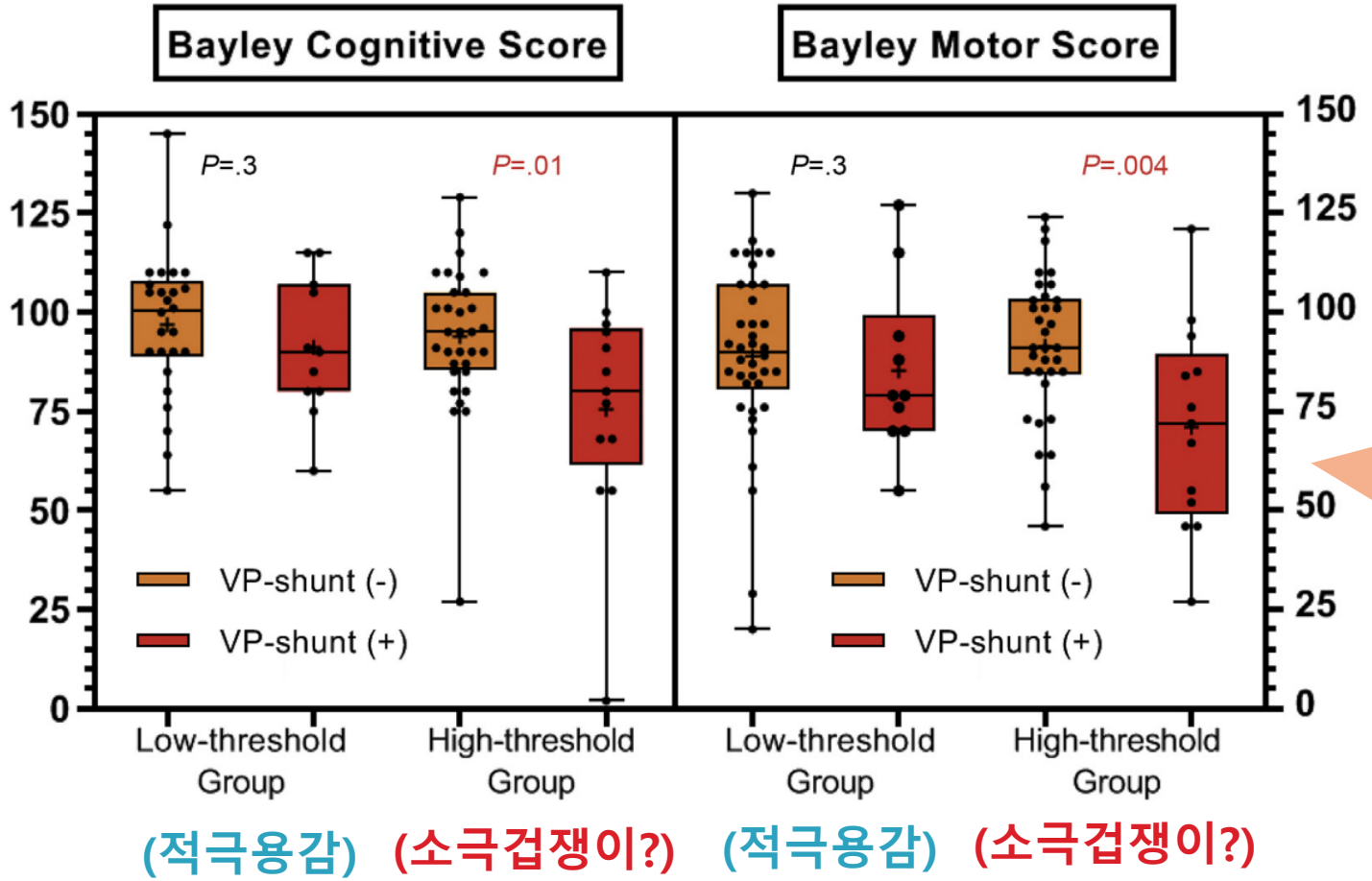
ELVIS trial follow-up



	(적극용감) Low-threshold group (n = 44)	(소극기다림) High-threshold group (n = 44)	*P* value
Gestational age at birth, weeks	28.1 ± 2.4	27.8 ± 2.7	.6*
Birth weight, g	1176 ± 361	1175 ± 404	.9*
Ventricular measurements on MRI, mm			
Ventricular width	13.4 (12.6-15.1)	15.9 (14.5-18.8)	**<.001**‡
AHW	6.6 (5.3-10.3)	10.6 (8.4-13.5)	**<.001**‡
FOH ratio	0.42 (0.4-0.46)	0.48 (0.43-0.51)	**.001**‡
Total Kidokoro score	8 (5-12)	12 (9-17)	**<.001**‡
Infants with grade III	7 (5-9)	10 (8-12)	**<.001**‡
Infants with grade III + PVHI	13 (7-19)	16 (15-19)	**<.001**‡
Kidokoro score severity			**.002**‡
Normal	3 (7)	0 (0)	
Mild	17 (39)	5 (11)	
Moderate	12 (27)	13 (30)	
Severe	12 (27)	26 (59)	

Cizmeci, J Pediatr 2019

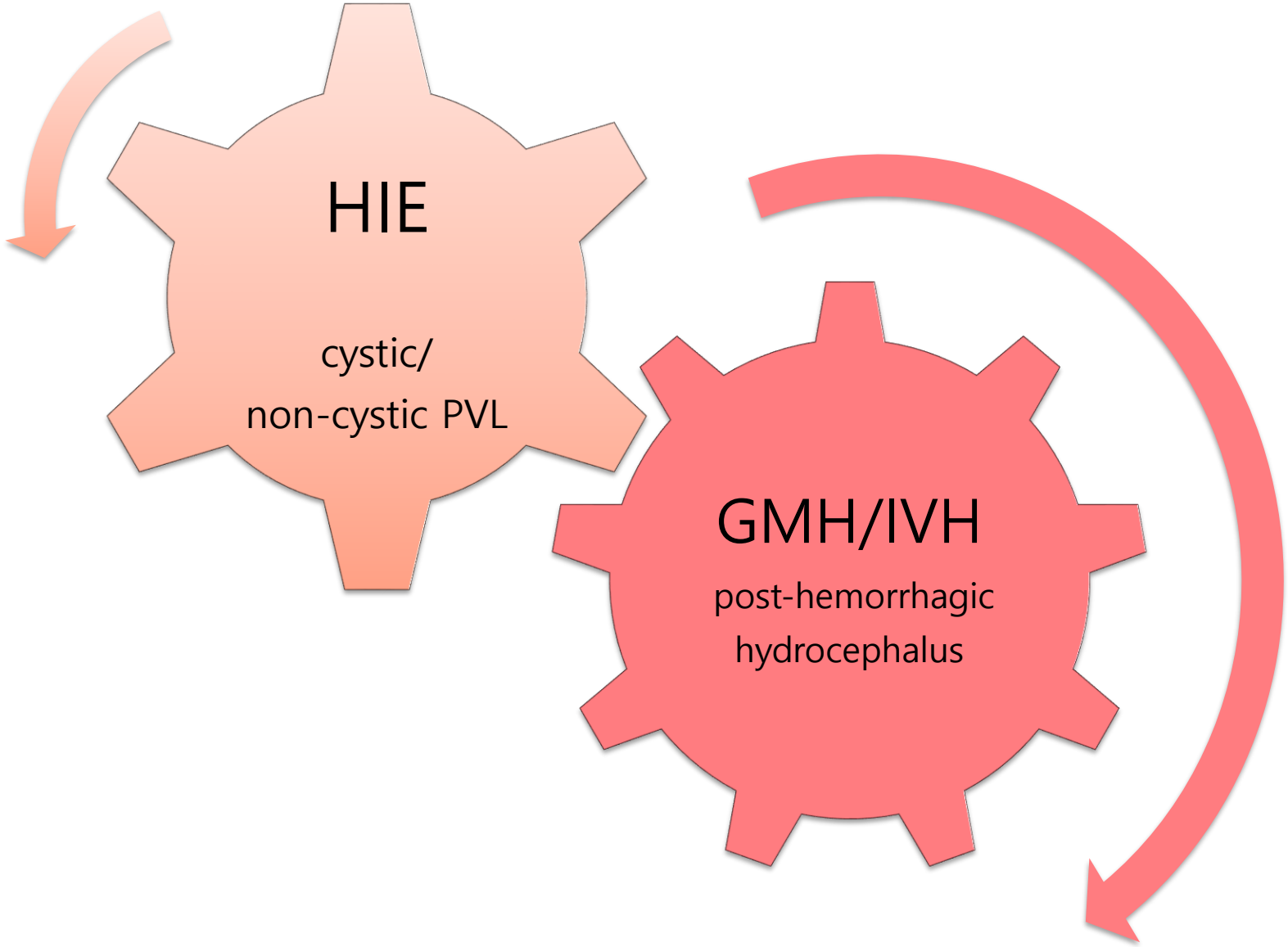
ELVIS trial follow-up



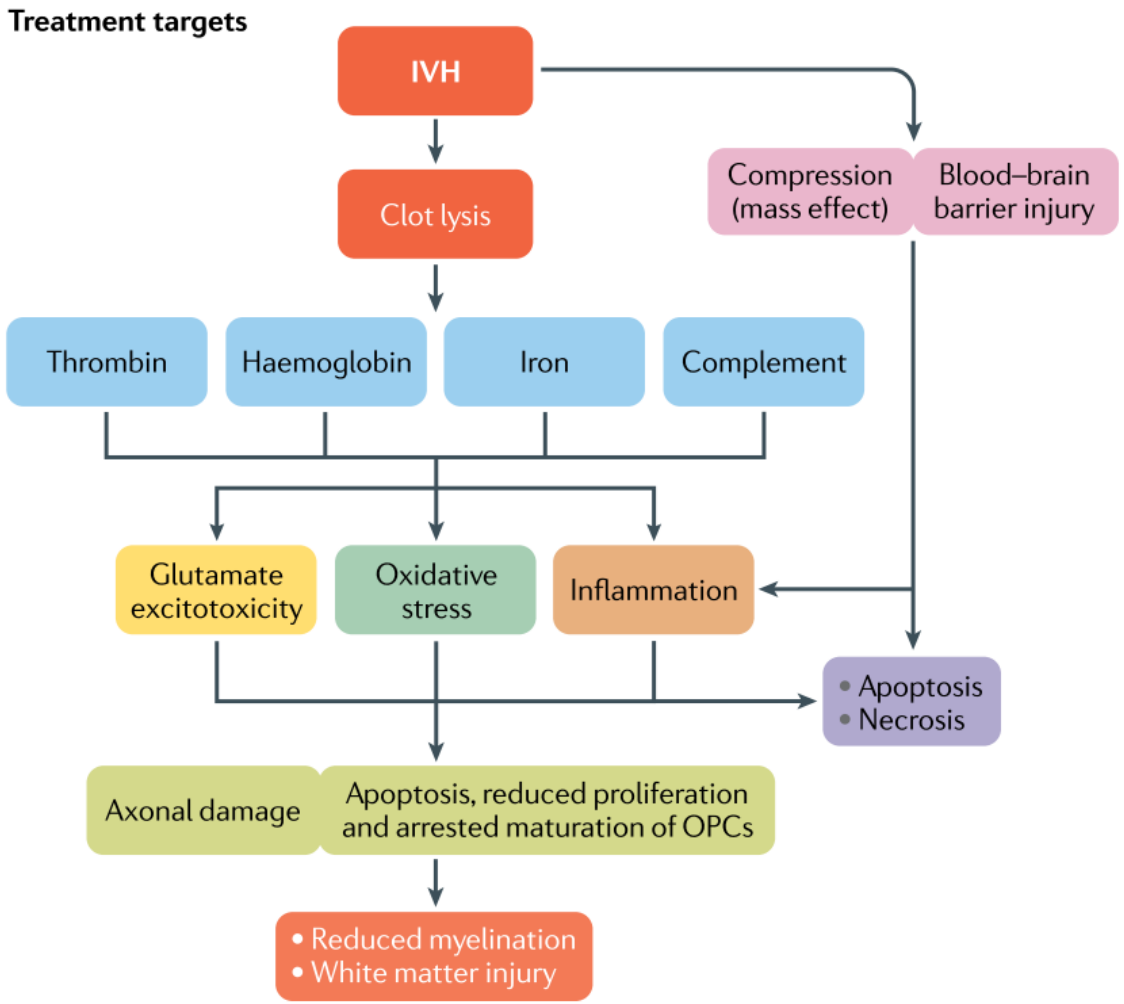
Death or BSID≤2SD:
35% vs 51%
(p=0.07)

Cizmeci, J Pediatr 2019

Encephalopathy of Prematurity



Treatment options for IVH and white matter injury



Mechanism-based treatments

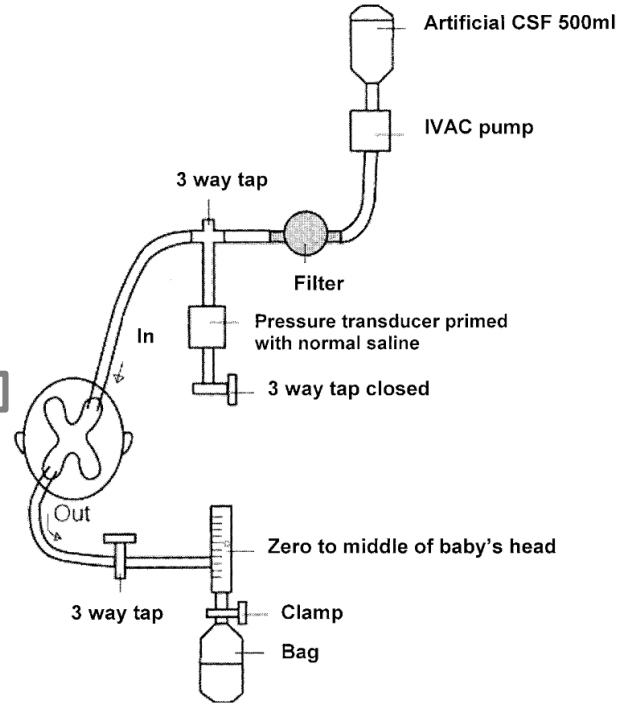
Surgical clot removal	Haemoglobin scavenger
Iron chelation	Thrombin antagonist
COX2 inhibitor	Iron chelation
Minocycline	Antioxidant
TNF antagonist	AMPA antagonist
Thyroxine	BMP inhibitor
Hyaluronidase	Stem cells

Ballabh, Nature Review 2021

Drain, irrigation and fibrinolytic therapy (DRIFT)

TABLE 2 **Trial Outcomes at 6 Months or First Discharge Home (When Later)**

Outcome	DRIFT ($N = 34$), n (%)	Standard Treatment ($N = 36$), n (%)	Difference (DRIFT − Standard), % (95% CI)	Relative Risk (95% CI)
VP shunt	13 (38)	14 (39; 1 dead)	−1 (−23 to 22)	0.98 (0.54 to 1.78)
Dead	2 (6)	5 (14)	−8 (−22 to 6)	0.42 (0.09 to 2.04)
Dead or shunt	15 (44)	18 (50)	−6 (−29 to 17)	0.88 (0.54 to 1.45)
Reservoir	13 (38)	27 (75)	−37 (−58 to −15)	0.51 (0.32 to 0.81)
Secondary IVH	12 (35)	3 (8)	27 (9 to 45)	4.24 (1.31 to 13.72)
Secondary infection	0 (0)	1 (3)		
Dead or shunt, by center				
Bristol	8/22 (36)	14/25 (56)	−20 (−48 to 8)	0.65 (0.34 to 1.25)
Katowice	6/10 (60)	4/10 (40)	20 (−23 to 63)	1.5 (0.60 to 3.74)
Glasgow	1/1	0/1		
Bergen	0/1	—		



2차 출혈!

Whitelaw, Pediatrics 2003, 2007

Drain, irrigation and fibrinolytic therapy (DRIFT)

- O: Developmental delay(cognitive/sensory motor) at 2YO

	Treatment		Severe Disability (<55)			
	DRIFT ($N = 35/34$),[a] n (%)	Standard ($N = 32$), n (%)	OR (95% CI)	P	OR (95% CI) Adjusted for Gender, Birth Weight, and Grade of IVH	P
MDI						
≥85	8 (23)	9 (28)	0.31 (0.11–0.86)	.024	0.17 (0.05–0.57)	.004
70–84	9 (26)	3 (9)				
55–69	7 (20)	1 (3)				
<55	11 (31)[b]	19 (59)[b]				
PDI						
≥85	4 (12)	5 (16)	0.54 (CI 0.20–1.45)	.22	0.21 (0.05–0.85)	.028
70–84	5 (15)	5 (16)				
55–69	11 (32)	4 (13)				
<55	14 (41)[b]	18 (56)[b]				

Whitelaw, Pediatrics 2010

Drain, irrigation and fibrinolytic therapy (DRIFT)

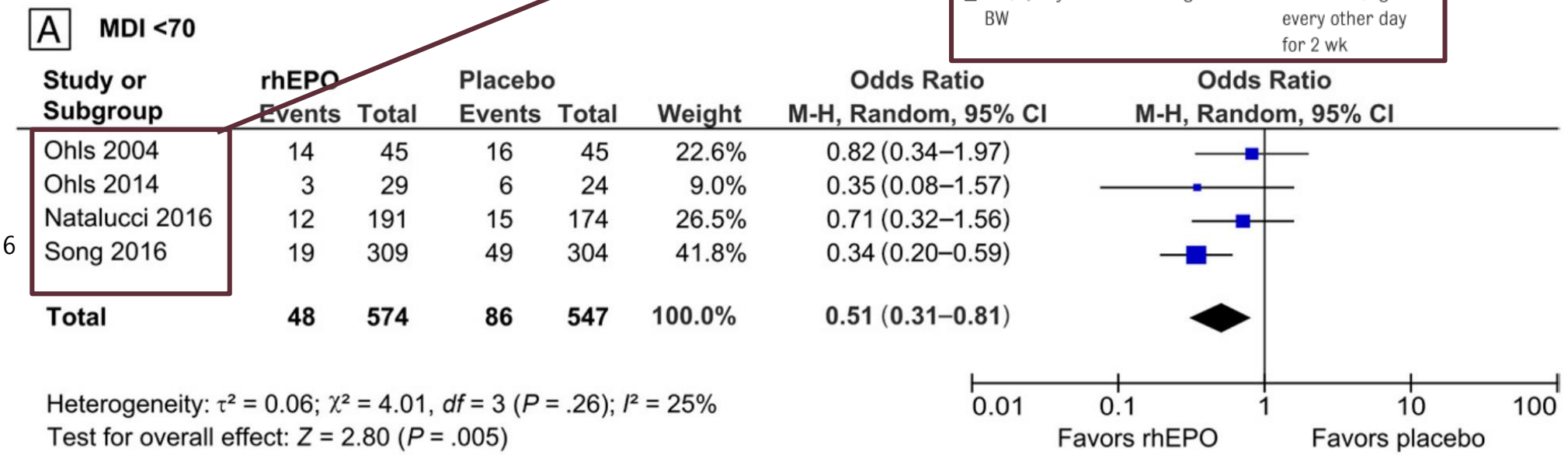
- O: Cognitive quotient (British Ability Scales and Bayley III scale) at 10 YO

Variable	n (DRIFT:standard)	DRIFT Mean (SD) or n (%)	Standard Mean (SD) or n (%)	Crude difference (95% CI), p value	Adjusted difference (95% CI), p value*
Primary outcome					
Cognitive ability quotient	27:24	69.33 (30.06)	53.68 (35.70)	15.65 (–2.86 to 34.16), 0.096†	23.47 (6.23 to 40.71), 0.009†
Sensitivity analyses					
Cognitive ability quotient‡	29:26	64.55 (34.04)	49.55 (37.22)	15.00 (–4.28 to 34.27), 0.125†	22.33 (4.77 to 39.89), 0.014†
Alive and without severe cognitive disability§	29:26	21 (72%)	11 (42%)	3.58 (1.16 to 11.04), 0.026¶	9.96 (2.12 to 46.67), 0.004¶
Alive and without severe cognitive disability**	32:31	21 (66%)	11 (35%)	3.47 (1.23 to 9.78), 0.019¶	7.69 (1.96 to 30.11), 0.003¶

Luyt & Whitelaw, Arch Dis Child Fetal Neonatal Ed 2020

Erythropoietin (EPO)

Gestational Age, Birth Wt	Time Point of Intervention	Intervention
≤32 0/7, ≤1000 g	24–96 h of age	rhEPO 400 IU/kg IV or SC, 3 times per wk until 35 0/7 wk gestation
Any GA,[b] 500–1250 g	≤48 h of age	rhEPO 400 IU/kg SC, 3 times per wk until 35 0/7 wk gestation
26 0/7–31 6/7, any BW	<3 h of age	rhEPO 3000 IU/kg IV at <3 h, 12–18 h and 36–42 h of age
≤32 0/7, any BW	<72 h of age	rhEPO 500 IU/kg IV every other day for 2 wk

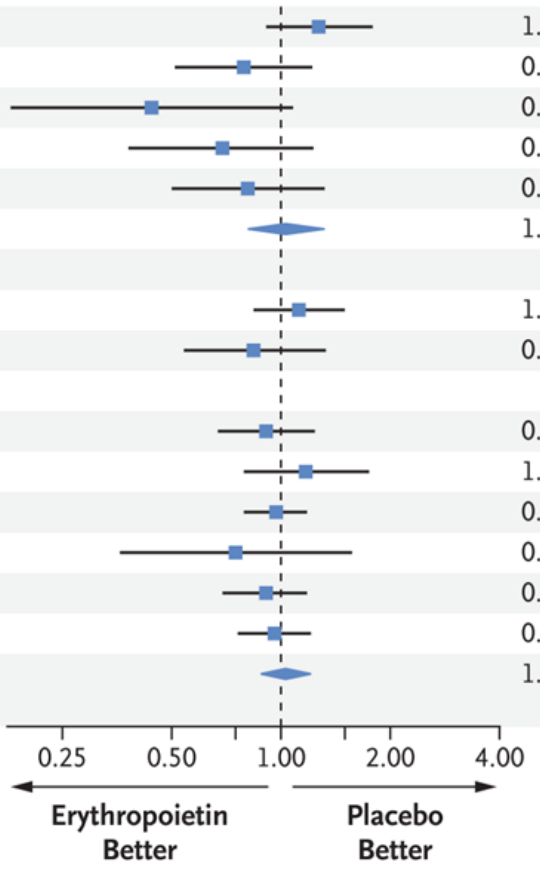


Pediatrics 2004
Pediatrics 2014
JAMA 2016
Ann Neurol 2016

Fischer, Pediatrics 2017

Erythropoietin (EPO)

Outcome	Erythropoietin	Placebo	Relative Risk (95% CI)
	no. of events/total no. (%)		
Death	63/476 (13)	50/460 (11)	1.27 (0.91–1.79)
Severe neurodevelopmental impairment	34/313 (11)	44/315 (14)	0.79 (0.51–1.22)
Severe cerebral palsy	8/313 (3)	18/315 (6)	0.44 (0.18–1.08)
Bayley-III composite cognitive score <70	19/311 (6)	28/314 (9)	0.69 (0.38–1.23)
Bayley-III composite motor score <70	28/310 (9)	36/314 (11)	0.81 (0.50–1.32)
Death or severe neurodevelopmental impairment	97/376 (26)	94/365 (26)	1.03 (0.81–1.32)
Gestational age at birth			
24 wk 0 days to 25 wk 6 days	67/190 (35)	62/197 (31)	1.12 (0.84–1.50)
26 wk 0 days to 27 wk 6 days	30/186 (16)	32/168 (19)	0.84 (0.54–1.33)
Sex			
Male	59/201 (29)	57/183 (31)	0.91 (0.67–1.24)
Female	38/175 (22)	37/182 (20)	1.17 (0.79–1.75)
Moderate-to-severe neurodevelopmental impairment	118/312 (38)	120/314 (38)	0.97 (0.79–1.18)
Moderate-to-severe cerebral palsy	13/311 (4)	18/315 (6)	0.75 (0.36–1.57)
Bayley-III composite cognitive score <85	77/311 (25)	87/314 (28)	0.91 (0.69–1.18)
Bayley-III composite motor score <85	95/310 (31)	96/314 (31)	0.96 (0.76–1.21)
Death or moderate-to-severe neurodevelopmental impairment	181/375 (48)	170/365 (47)	1.03 (0.88–1.21)

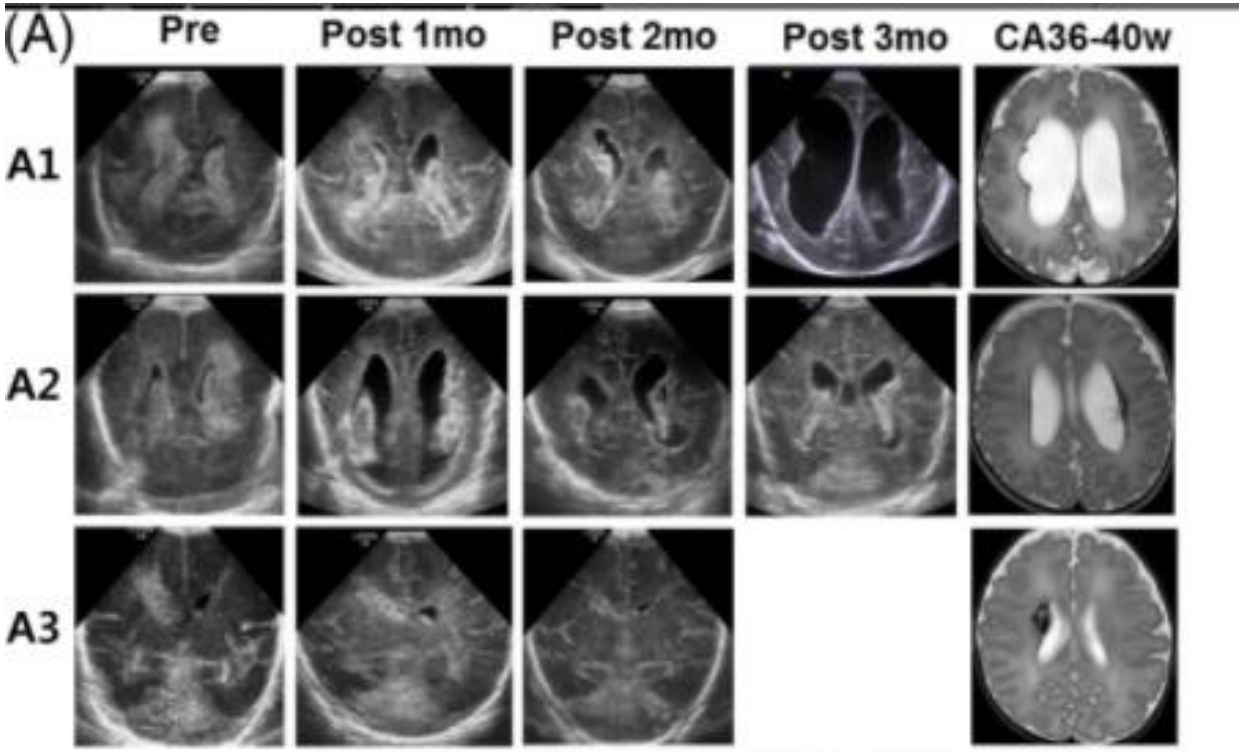


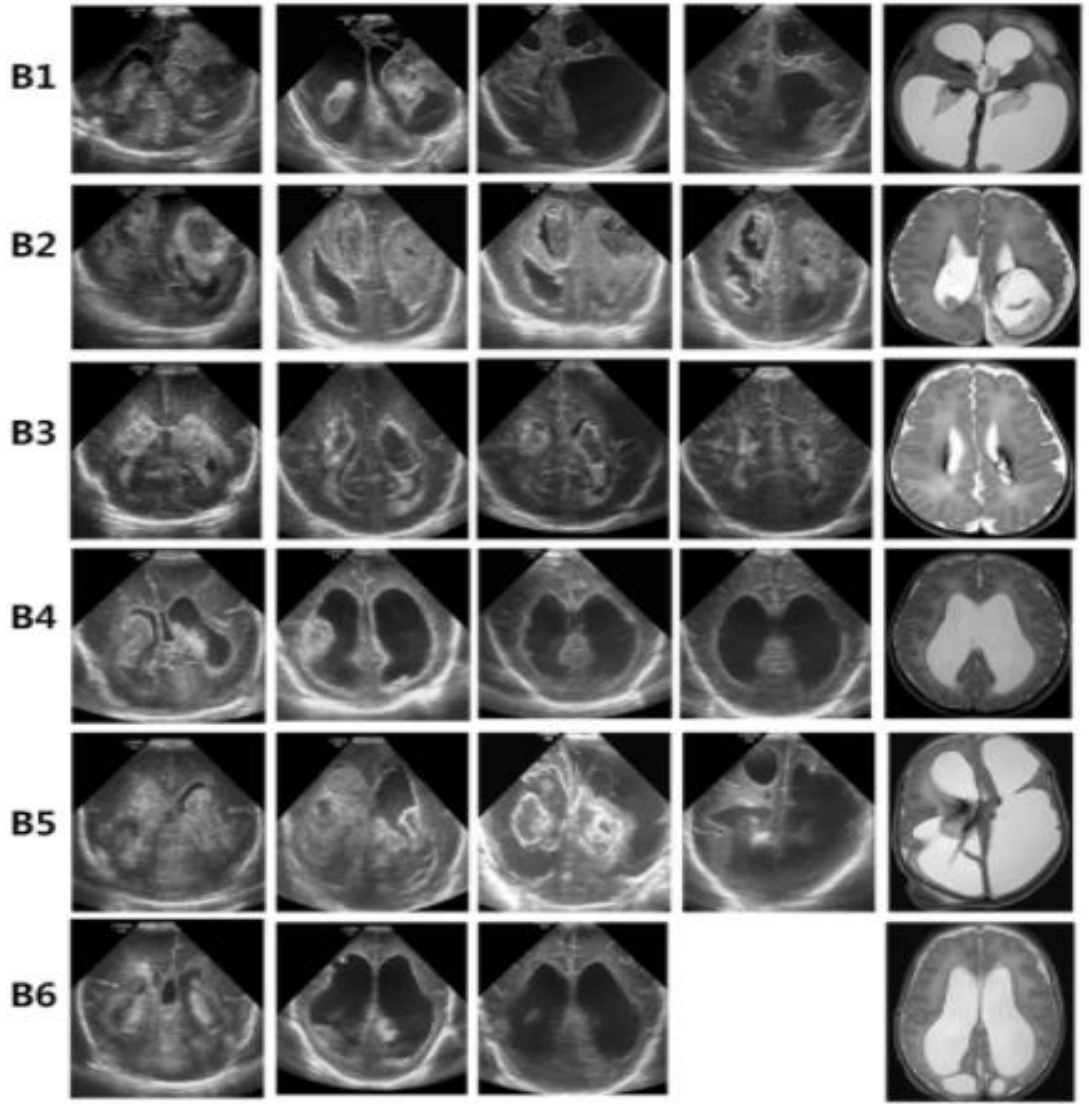
PENUT trial

- P: 24/0-27/6 weeks
- I: <24h, EPO 1000 -> 400 IU/kg, until 32 weeks
- O: death or severe NDI at 22 to 26 mo of PMA

Juul, NEJM 2020

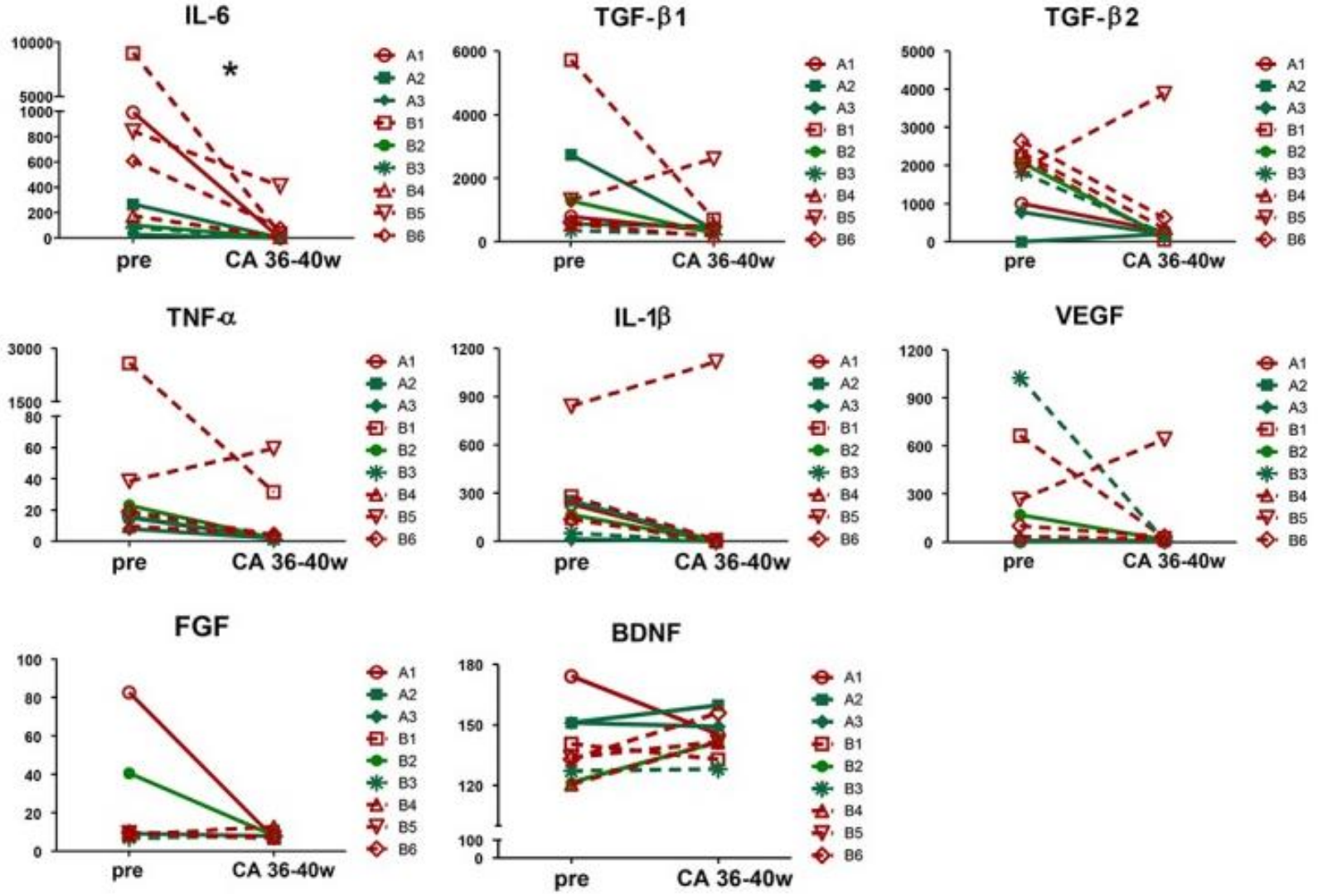
Stem cell for severe IVH (grade 4)





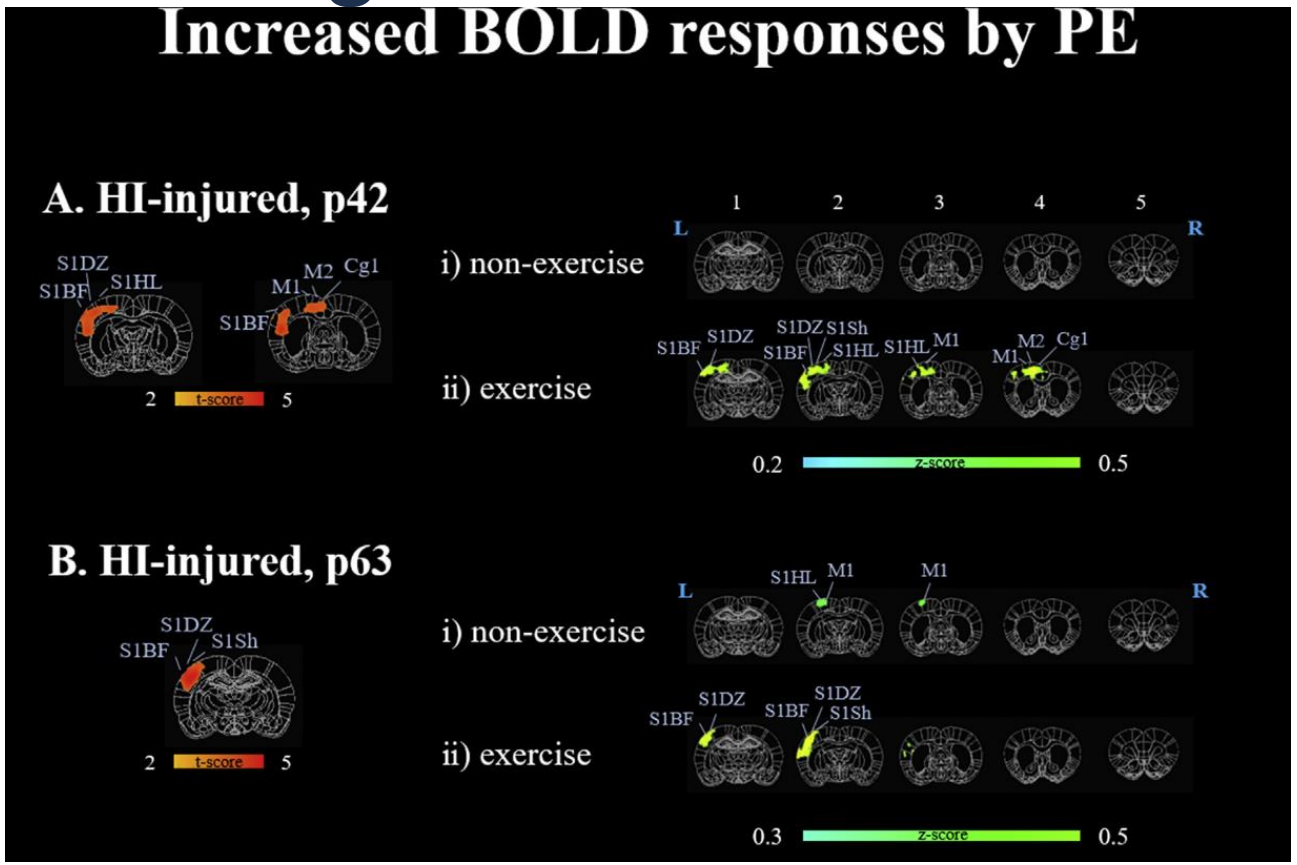
Ahn SY, Stem Cells Transl Med . 2018

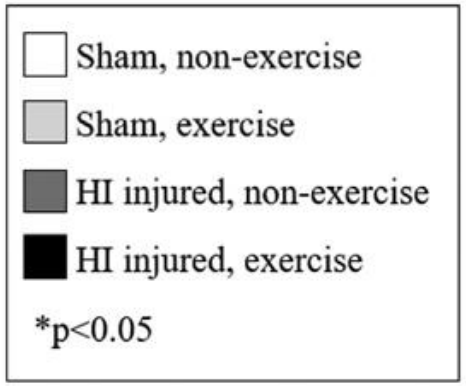
Stem cell for severe IVH (grade 4)

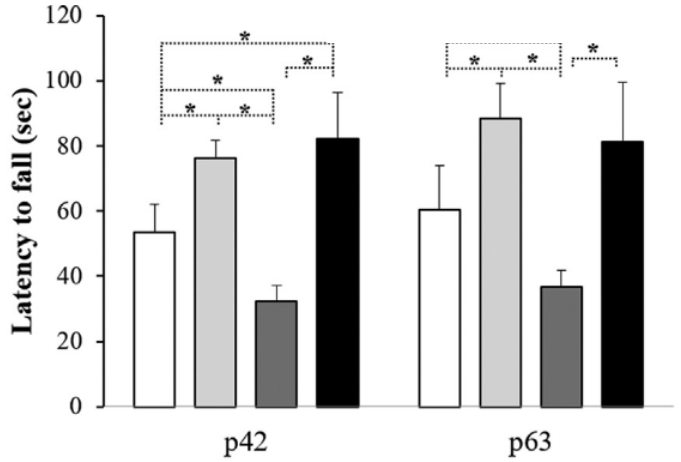


Ahn SY, Stem Cells Transl Med 2018

Lifelong rehabilitation







injury. In summary, the results of the current study indicate that PE, even if performed beyond the critical period or during adulthood, can be an effective therapy to treat neonatal brain injuries, providing a potential mechanism for the development of a potent rehabilitation strategy to alleviate HI-induced neurological impairments.

Chae, Kim, Neuroimage 2019

In summary

- 미숙아 출생 증가 및 생존률 증가로 합병증 발생 확률은 오히려 증가한다.
- 뇌출혈을 줄이고자 하는 여러 노력이 시행 중이다.
- 새로운 도전과 함께 지속적인 재활치료가 미숙아 신경학적 발달에 중요하다.

Thank you for attention

感謝
ありがとうございます

“A person is a person, no matter how small.”
- Horton, Dr. Seuss