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ORIGINAL ARTICLE

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

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Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *Objetivo:*
  - *Revisar la evidencia sobre las comorbilidades relacionadas con la EUGR durante la infancia mediante un enfoque sistemático*

- *Método:*
  - *Revisión se realizó en las data de MEDLINE y EMBASE, hasta septiembre de 2017*
  - *Se incluyeron publicaciones que mostraban evidencia sobre las comorbilidades asociadas con la EUGR en recién nacidos prematuros.*
  - *Se excluyeron las publicaciones cuando no encajaban en el marco conceptual del estudio y los que evaluaron los cambios en el crecimiento intra / extrahospitalario sin definir específicamente la EUGR.*

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

Fig. 1 Flowchart showing the flow of studies from identification to extraction of data from the included studies

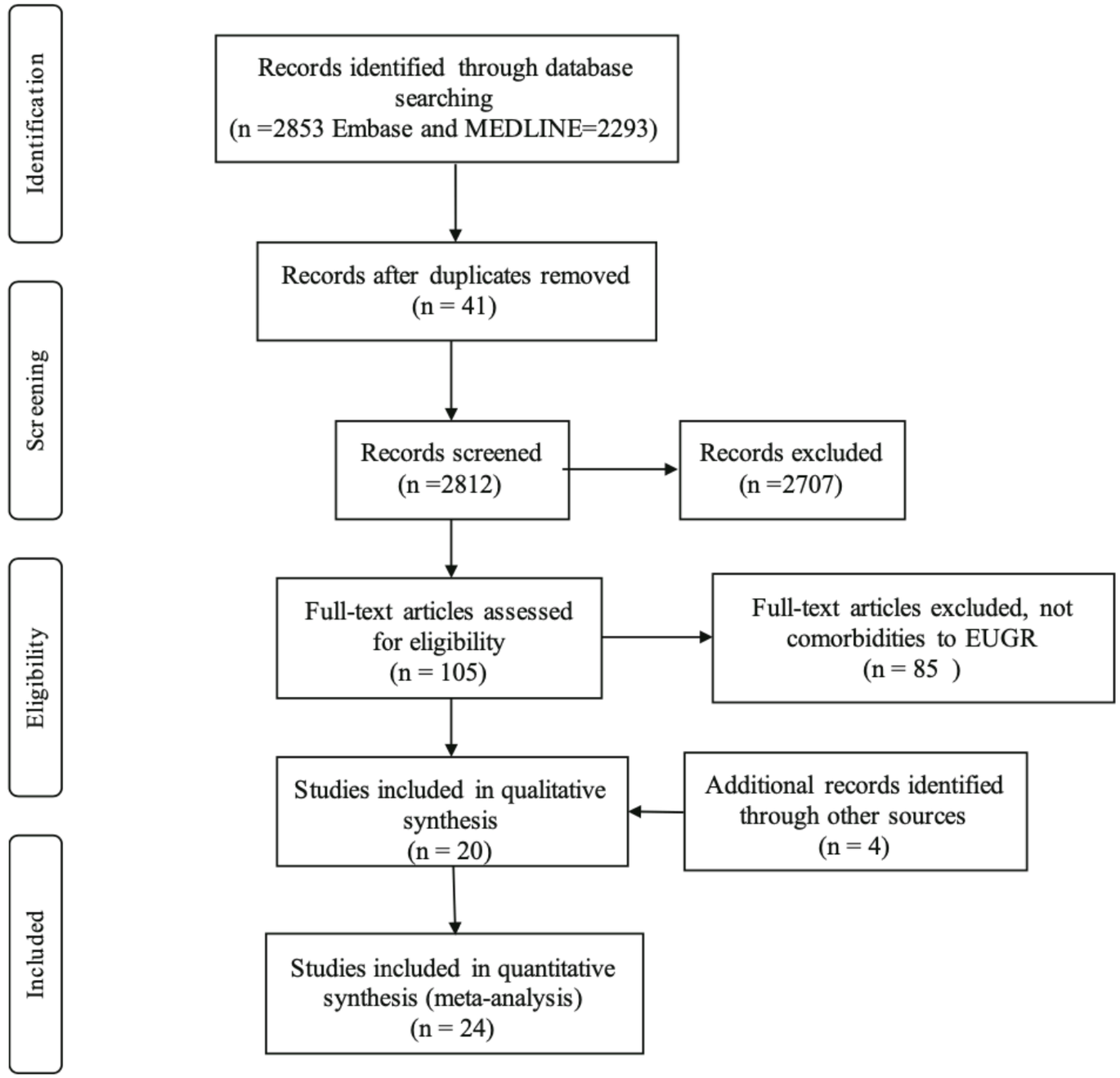

Table 4 Comorbidities of growth

Author	Type of study	Sample size (*n*)	Definition of EUGR	Growth chart at birth	Child growth chart	Comorbidities of growth
Hack et al., 1982[7]	Cohorts	192 VLBW	"Extrauterine growth failure" < − 2 DS W NB, 40 w and 8 m	Babson and Benda, 1976	Babson and Benda, 1976	The NB AGA with EUGR at 40 w and 8 m, the NB AGA with EUGR at 8 m and the NB SGA with EUGR at 8 m compared with those that are not EUGR have lower HC at 8 m: 45.1 + − 1, 6 cm vs 43.4 + − 1.1 cm/44.5 + − 1.6 cm vs 42.6 + − 1.7 cm/44.1 + − 1.7 cm vs 42.7 + − 1.5 cm
Tudehope et al., 1983[31]	Cohorts	164 ELBW: 131 AGA/33 SGA	"Postnatal growth failure": W < 2 DS at discharge	Usher- McLean, 1969	National health and medical research council curves	24 vs 64% of AGA vs SGA are EUGR and persist at 20 vs. 36%, respectively.
Hack et al., 1991[8]	Cohorts	249 VLBW	"Growth failure": HC < − 2 DS NB at 40 weeks, 8 months, and 8 years	Roche, 1987	Roche, 1987	12% abnormal HC (< − 2 DS) at birth, 23% at 40 w, 13% 8 m and 8% at 8 years
Finken et al., 2006[5]	Cohorts	380 VLBW	"Growth restraint": NB AGA whit W y/o L < − 2 DS at 3 m AC	- RN: Niklasoon, 1991. - Postnatal: Fredriks, 2000.	Fredriks, 2000.	SGA and EUGR with L < − 2 SD at 5 years have a risk of 90% adult L (19 years, < − 2.5 DS)
Cheong et al., 2008[2]	Cohorts	227 (NB < 1250 g or < 30 weeks)	"Poor postnatal growth": difference Z-score between two points NB, at the age of term and 2 years; Microcephaly: HC < − 2DS	Cole, 1998	Cole, 1998	7.5% at term age and 29.7% at 2 years have microcephaly. Microcephaly is correlated with lower cerebral volume, especially of the deep nuclei of the grey matter.
Roggero et al., 2008[26]	Cohorts	61 (NB < 1800 g and 34 w/AGA): 35 EUGR/26 no-EUGR	"Growth retardation": < 2 DS Z-score to the age of term	Delemarre, 2007	Agostini et al., 2000	Up to 3 m the EUGR present lower W/L/HC/fat mass but the growth increases and equals to 4–5 m compared to non-EUGR ($p < 0.05$) 19.6% EUGR of HC at 3–4 years
Kon et al., 2010[13]	Cohorts	38 VLBW: 16 EUGR/22 No-EUGR	"Extrauterine growth restriction": W $p < 10$ at discharge	Japan (they do not provide reference)	Not indicated	At 18 m they have lower W and L ($p < 0.001$): - W: 9.2 ± 1.1 vs 9.9 ± 0.087 kg - L: 78 ± 3.4 vs 80.8 ± 3 cm
Ortiz-Espejo et al., 2012[20]	Case-control	161 prepubertal: 38 EUGR/123 no-EUGR	"Extrauterine growth restriction": NB W > p 10 and W $p < 3$ at 36 w and at discharge	Carrascosa, 2008	Hernández, 1988	Z-score lower in EUGR prepubertal than no-EUGR: - L: 0.44 ± 0.86 vs 0.27 ± 0.79 - W: 0.45 ± 0.97 vs 0.08 ± 0.69 - BMI: 0.4 ± 1.05 vs − 0.16 ± 0.46
De Jesus et al., 2013[3]	Cohorts	2971 (NB < 27 weeks): 385 (13%) SGA, 2586 No-SGA	"Postnatal growth failure": W or L < p 10 at 36 weeks	Olsen, 2010	OMS, 2006	Greater EUGR in SGA than in non-SGA (97.8% vs. 76.6 $p < 0.001$) and lower HC ($p < 10$ to 36 weeks): in SGA than in non-SGA: 87 vs. 42% $p < 0.001$. Remaining the difference at 18-22 m W/L/HC ($p < 0.001$) in SGA versus non-SGA: 60%, 40.5%, 44.9% vs. 37.4%, 21.9, 21.9%, respectively
Ortiz-Espejo et al., 2013[21]	Cohorts	161 prepubertal: 38 EUGR/123 no-EUGR	"Extrauterine growth restriction": NB W > p 10 and W $p < 3$ at 36 w and at discharge	Carrascosa, 2008	Hernández, 1988	33% of EUGR have W < p 10 in the prepubertal stage
Pampanini et al., 2015[23]		103 (NB < 34 weeks)		Bertino, 2010	- Cacciaria et al., 2006.	- Early childhood (2–6.9 years) are EUGR: 13.6% W (worse in men 17% than in women 10%), 12.6% L

Table 4 (continued)

Author	Type of study	Sample size (*n*)	Definition of EUGR	Growth chart at birth	Child growth chart	Comorbidities of growth
	Cohorts multicéntri-c (4)		"Severe extrauterine growth retardation": W and/or L − 2 DS Z-score at discharge		- HC: OMS, 2010	(7.7% have − 2.5 DS), 19.6% HC and BMI 18.4% (22.7% men and 12% women). - L at the term age was the greatest predictor of L in childhood (r^2 0.34, $p < 0.001$).
Ruiz del Prado et al., 2016[27]	Cohorts	82 (NB < 35 weeks and < 2200 g)	"Postnatal growth restriction" $p < 10$ W, L, and HC Z-score at discharge and 6 m	Carrascosa, 2008	- Carrascosa, 2008 - HC: OMS, 2010	At birth the percentage of PT with $p < 10$ are: 24.4% W, 22.7% L, and 22.2% WC. On discharge are EUGR: 44.9% W, 43.8% L, and 32.4% HC. At 6 m persists $p < 10$: W 11.9%, L 7.1%, and HC 2.16% (recover it especially the late preterm)
Raaijmakers et al., 2017[25]	Cohorts	140 (NB < 1000 g and < 33 w)	"Extra–uterine growth restriction": Do not achieve catch-up growth between two points (Z-score 0.67)	Flanders, 2006	Flanders, 2006	- EUGR 2 years: 90.1% W, 86.3% L, and 85.9% HC. - EUGR 11 years: 8.5% W, 15.6% L, and 61.5% HC. - The percentage of fat mass in adolescents varies according to reach the catch up of W and L in the first 2 years or not (16.8% vs 25.7% $p < 0.001$/20.9% vs 25.8%, $p = 0.049$, respectively)

AGA appropriate for gestational age, *AC* corrected age, *BMI* body mass index, *ELBW* extremely low birth weight, *EUGR* extrauterine growth restriction, *HC* head circumference, *L* length, *NB* new born *SGA* small for gestational age, *VLBW* very low birth weight, *W* weight

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *13 artículos se centraron en el crecimiento de los niños con EUGR:*
- *Mostraron un porcentaje variable de EUGR:*
  - *Peso: 13.6– 90.1%*
  - *Talla: 7.1–86.3%*
  - *CC: 2.16– 85,9%*
- *Los niños que presentaron menor edad gestacional y peso mostraron mayor alteración.*

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *Esta situación también continuó a lo largo de la etapa prepuberal, con un peso <p10 persistente en el 33% de los niños con antecedentes de EUGR*

- *La EUGR persistente a los 5 años de edad (longitud inferior a -2 DE) conlleva un 90% de riesgo de talla baja en la edad adulta (inferior a 2.5 DE).*

- *PEG tiene un mayor porcentaje de EUGR que los AEG (97.8 vs 64%), y la diferencia persiste hasta los 22 meses de edad*

Table 5 Comorbidities in the neurodevelopment of children with extrauterine growth restriction

Author	Type of study	Sample size (*n*)	Definition of EUGR	Growth chart at birth	Comorbidities in the neurodevelopment	Neurodevelopment chart
Hack et al., 1982[8]	Cohorts	192 VLBW	"Extrauterine growth failure" < − 2 DS W RN, 40 weeks and 8 months	Babson and Benda, 1976	The NB AGA with EUGR at 40 w and at 8 m and the SGA with EUGR at 8 m compared with those that are no-EUGR have a lower IQ score (109 ± 14 vs 89 ± 22; 108 ± 20 vs 93 ± 17; 106 ± 19 vs 99 ± 18, p 0.005 and greater sensorineural disability * 46% vs 9%, 27% vs 12%, 32% vs 13%, $p < 0.01$.	BSDI-II
Tudehope et al., 1983[31]	Case-control	164 ELBW: 131 AGA/33 SGA	"Postnatal growth failure": W < 2 DS at discharge	Usher- McLean, 1969	No differences in neurodevelopment 1, 3, and 4 years. EUGR is not predictive of neurodevelopment.	Griffithi's mental development scale score, McCarthey scale of children's abilities
Hack et al., 1991[7]	Cohorts	249 VLBW	"Growth failure": HC < − 2 DS NB, 40 weeks, 8 months, and 8 years.	Roche, 1987	Abnormal PC at 8 m is an independent predictor (socioeconomic and neonatal risks) of adverse effects at 8 y in IQ (RR 1.8 (1.12–1.9 $p < 0.05$; 46.2% vs 25.6% for IQ < 85, IQ < 70 RR 5.74 (1.36–24.33, $p < 0.01$)/receptive language differences of 1.8 points (0.56–3.18, $p < 0.01$), spoken differences of − 3.7 points (− 5.26 to − 2.19, $p < 0.05$). In addition, they have greater hyperactivity 3.9 points difference (6.79–0.95, $p < 0.05$)) and limitations on academic skills (reading, math or spelling, score < 80) RR 1.81 (1.25–2.61, $p < 0.01$)	- Receptive language: Token test part V, Spoken: Fletcher test Behavior: Achenbach child behavior checklist Academic skills: Woodcock Reading Mastery Test, Woodcock-Johnson psycho-educational battery and wide-range achievement test.
Shah et al., 2006[28]	Cohorts	74 (NB < 28 w)	"Post-natal growth failure": difference Z-score birth at 36 weeks > 2 DS	Kramer, 2001	At 18 m, children with HC < 2 SD have worse PDI than children with HC superirors (74 ± 14 vs 86 ± 14 $p < 0.04$) although HC does not predict MDI.	BSDI-II
Cheong et al., 2008[22]	Cohorts	227 (NB < 1250 g or < 30 weeks) (186 RMN cerebral)	"Poor postnatal growth": difference Z-score between two points NB, at the age of term and 2 years; Microcephaly: HC < − 2DS	Cole, 1998	Microcephaly at 2 years is correlated with poor cognitive development (MDI < 70: 33%, $p < 0.001$), motor (PDI < 70: 22%, $p < 0.001$) and palsy cerebral (15%, p 0.003).	BSDI-II
Hök-Wikstrand et al., 2009[10]	Cohorts	66 VLBW	"Poor postnatal growth": DS W of birth at 32 w	Marshal, 1996	The DS score of the HC is the only at 5 years predictor of visual acuity for visual impairment OR: 0.25 (95% CI 0.09–0.7). Poor visual perception at 5 y is related to low weight at 32 w (SDS) (r 0.38, p 0.036) and low HC (SDS) in follow-up up to 5 years (r 0.39, $p = 0024$)	Visual perception skills test, 1996. Poor visual acuity (< 0.3)
Kon et al., 2010[13]	Cohorts	38 VLBW: 16 EUGR/22 No EUGR	"Extrauterine growth restriction": W $p < 10$ at discharge	Japonesa (they do not provide reference)	- 18 m < PDI 92.6 ± 11.2 vs 99.5 ± 11.2, $p < 0.005$ in EUGR than in non-EUGR, no differences in MDI. - Correlation between iron levels first m and PDI at 18 m ($p = 0.01$)	BSDI-II

Table 5 (continued)

Author	Type of study	Sample size (*n*)	Definition of EUGR	Growth chart at birth	Comorbidities in the neurodevelopment	Neurodevelopment chart
Neubauer et al., 2016[17]	Cohorts	273 VLBW	"Poor postnatal growth": Suboptimal HC < 1 DS and microcephaly > − 2 DS	- Fenton, 2013 - 2 years: Haschke, 2000 - 5 years: Prader, 1989	Suboptimal HC at 3, 18 and 24 m predicted low IQ at 5 y (E 57.1% / S 73.4% / PPV 27.4% / NPV 90.7%). Suboptimal HC at 3 m have 10% less IQ at 5 years (average 90 points [20–122] vs 98 points [20–138], $p = 0.001$)	Wechster Preschool and Primary Scales of Intelligence, 3ª ed.
Raaijmakers et al., 2017[25]	Cohorts	140 (ELBW and < 33 weeks)	"Extrauterine growth restriction": Do not achieve catch-up growth between two points (Z-score 0.67)	Flanders, 2006	Catch up is not associated with worse neurodevelopment valued up to 11 years.	- BSDI-II - Wechsler Non–Verbal test

AGA appropriate for gestational age, *AC* corrected age, *BSDI* scales of Bayley Infant Development, *ELBW* extremely low birth weight, *EUGR* extrauterine growth restriction, *HC* head circumference, *IQ* intelligence quotient, *L* length, *MDI* mental development index, *NB* new born, *PDI* psychomotor development index, *SGA* small for gestational age, *VLBW* very low birth weight, *W* weight

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *NEURODESARROLLO*
- *7 artículos (1045 RN MBPN) encontraron una asociación significativa entre el neurodesarrollo y la EUGR*
- *CC subóptima tenía puntuaciones más bajas:*
  - *Coeficiente intelectual: <70: 33%; p = 0.001*
  - *Índice de desarrollo psicomotor: <70: 22%; p = 0,001*

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- *NEURODESARROLLO*
- *Una CC anormal a los 8 meses es un predictor independiente de efectos adversos a los 8 años, lo que resulta en un riesgo 5.7 veces mayor de obtener un puntaje <70 en una prueba IQ(RR 5.74 (1.36–24.33) y deficiencias en el lenguaje receptivo / hablado*
- *La microcefalia a los 2 años se correlaciona con la parálisis cerebral (15% (p = 0.003)*

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *CARDIOVASCULAR*
- *8 artículos*
- *En la etapa prepuberal los niños con EUGR tienen PAS y PAD más altas que los no-EUGR (p 0,001) [20].*
- *Casi la mitad de esos niños eran hipertensos*
- *Los niños con EUGR tienen un colesterol HDL más bajo y niveles plasmáticos glucémicos más altos, pero sin relevancia clínica*

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *OTROS:*
- *Se han demostrado efectos negativos sobre el sistema antioxidante*
- *Los niños con antecedentes de EUGR han mostrado niveles más bajos de hemoglobina y ferritina durante los primeros meses de vida y en la etapa prepuberal, pero sin importancia clínica*
- *Los recién nacidos prematuros con peso p <10 a la edad de término, en comparación con aquellos con peso> p10, tenían un riesgo 7,8 veces mayor (IC del 95%: 1,2-50,1, p <0,03) de defectos en la dentición primaria (opacidades e hipomielinización), especialmente en los incisivos*

Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review

- *Conclusiones:*
  - *La evidencia disponible sugiere que EUGR se asocia fundamentalmente con:*
    - *Retraso en el peso, la altura y la circunferencia de la cabeza en la infancia,*
    - *Disminución del desarrollo neurológico*
    - *Riesgo cardio-metabólico.*
- *Mejorar el conocimiento sobre esta enfermedad podría contribuir a mejorar la atención al paciente.*
- *Por lo tanto, es necesario realizar estudios aleatorizados multicéntricos basados en criterios bien definidos de EUGR para aumentar el número de pacientes incluidos en los estudios observacionales, así como replicar los resultados obtenidos en diferentes poblaciones.*

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ORIGINAL ARTICLE

Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

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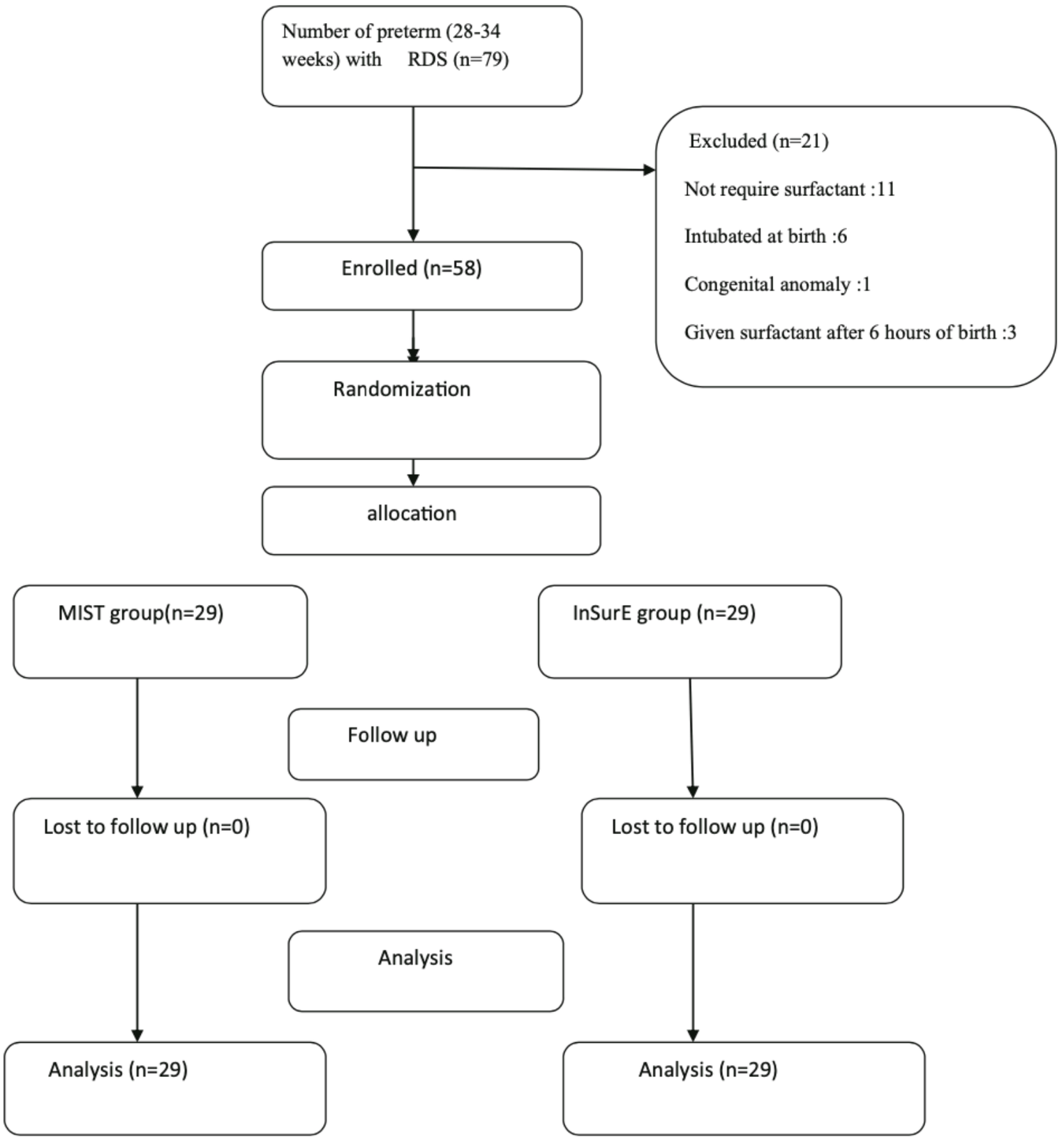
Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

- *Objetivo:*
  - *Comparar la eficacia de la técnica MIST e InSurE en NIPPV como soporte respiratorio primario entre los lactantes con SDR con edad gestacional de 28 a 34 semanas.*

- *Método:*
  - *Estudio randomizado*
  - *UCIN nivel III en un hospital de atención terciaria en Kolkata, India*
  - *Desde marzo de 2019 hasta diciembre de 2019.*
  - *Los RN con edad de gestación de 28 a 34 semanas con diagnóstico de SDR fueron ingresados.*
  - *Se excluyeron los lactantes con anomalías congénitas importantes, asfixia perinatal y aquellos que requirieron intubación en la sala de partos.*

Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

- *Intervención:*
  - *Se ingresaban con NIPPV: PIM 12-15, PEEP de 5-6, FR 40.*
  - *Los RN con FiO2 más del 30% en NIPPV para mantener la saturación entre el 90 y el 95% en las primeras 6 h de vida fueron aleatorizados para recibir surfactante mediante la técnica MIST o InSurE.*
- *Usaron curosurf 200 mg/kg*
- *Outcome primario: necesidad de VMI a las 72h de vida*
- *Outcome secundarios: DAP, HIV > grado II, DBP, DBP/ muerte antes del alta, duración de la hospitalización*


Number of preterm (28-34 weeks) with RDS (n=79)
Excluded (n=21)
Not require surfactant :11
Intubated at birth :6
Congenital anomaly :1
Given surfactant after 6 hours of birth :3
Enrolled (n=58)
Randomization
allocation
MIST group(n=29)
InSurE group (n=29)
Follow up
Lost to follow up (n=0)
Lost to follow up (n=0)
Analysis
Analysis (n=29)
Analysis (n=29)

Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

Table 1 Baseline variables of the enrolled subjects

Variable	MIST (n = 29)	InSurE (n = 29)	p value
Gestation age, weeks mean (sd)	30.07 (1.51)	29.90 (1.67)	0.68
Birth weight, g, mean (sd)	1225 (281)	1222 (322)	0.97
Male, n (%)	18 (62.07)	18 (62.07)	1
Antenatal steroid (any dose) n (%)	23 (79.31)	24 (82.76)	1
Antenatal steroid (complete course with 4 doses), n (%)	1 (3.44)	3 (10.340	0.61
Multigravida, n (%)	6(20.68)	6 (20.68)	1
Caesarean section delivery, n (%)	19 (65.52)	16 (55.17)	0.59
Apgar 5 min (1–10), median (IQR)	8 (7–9)	8 (7–9)	0.24
FiO2 before surfactant therapy,%, median (IQR)	50 (35–60)	45 (40–55)	0.59
Time of birth to surfactant therapy, h, median (IQR)	1 (1–2)	1 (1–2)	0.82
CRIB-II scores, mean (sd)	6.24 (2.66)	6.31 (2.48)	0.91
SpO_2 /FiO_2 ratio before surfactant, median (IQR)	186 (184–206)	202 (184–204)	0.90

Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

- *Ambos grupos fueron comparables con las variables basales.*

- *La edad promedio fue de 30 semanas.*

- *Observamos una alta proporción de partos por cesárea (55-65%).*

- *El tiempo promedio de requerimiento de surfactante desde el nacimiento fue de 1 h.*

Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

Table 2 Outcome variables of the two groups—MIST and InSurE

Variable	MIST (n = 29)	InSurE (n = 29)	Relative risk (95% confidence interval)	p value
Invasive mechanical ventilation, n (%)	3 (10.34)	6 (20.69)	0.62 (0.22–1.32)	0.47
Hemodynamically significant patent ductus arteriosus, n (%)	6 (20.69)	8 (27.58)	0.82 (0.39–1.45)	0.76
Intraventricular haemorrhage > grade 2, n (%)	0 (0)	1 (3.45)	0.00 (0.00–1.64)	> 0.99
Bronchopulmonary dysplasia, n (%)	4 (13.79)	8 (27.59)	0.61 (0.24–1.22)	0.17
Bronchopulmonary dysplasia/mortality before discharge, n (%)	4 (13.79)	9 (31.03)	0.55 (0.22–1.12)	0.11
Second dose of surfactant, n (%)	3 (10.3)	2 (6.89)	1.22 (0.45–2.08)	> 0.99

Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial

- *Conclusiones:*
  - *No había diferencia de necesidad de VMI en MIST en comparación con InSurE si usamos NIPPV.*
  - *No hubo diferencia en el resultado compuesto de DBP / mortalidad (RR con MIST, 0.55; IC 95%, 0.22 a 1. 22) y DBP entre los sobrevivientes (RR con MIST 0.61; IC 95%, 0.24 a 1.22) entre dos grupos*
  - *No hubo diferencia estadística en el requerimiento en la segunda dosis de surfactante (Tres bebés en el grupo InSurE y dos bebés en el grupo MIST)*
  - *En el presente estudio, los bebés del grupo MIST también mostraron menos hospitalización. La diferencia también fue estadísticamente significativa*
  - *El tamaño de la muestra también fue pequeño con baja potencia calculada post hoc. Todo esto puede producir sesgos en los resultados.*