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L'administration d'une tocolyse après une rupture prématurée des membranes avant terme permet-elle d'améliorer le pronostic de l'enfant prématuré ?

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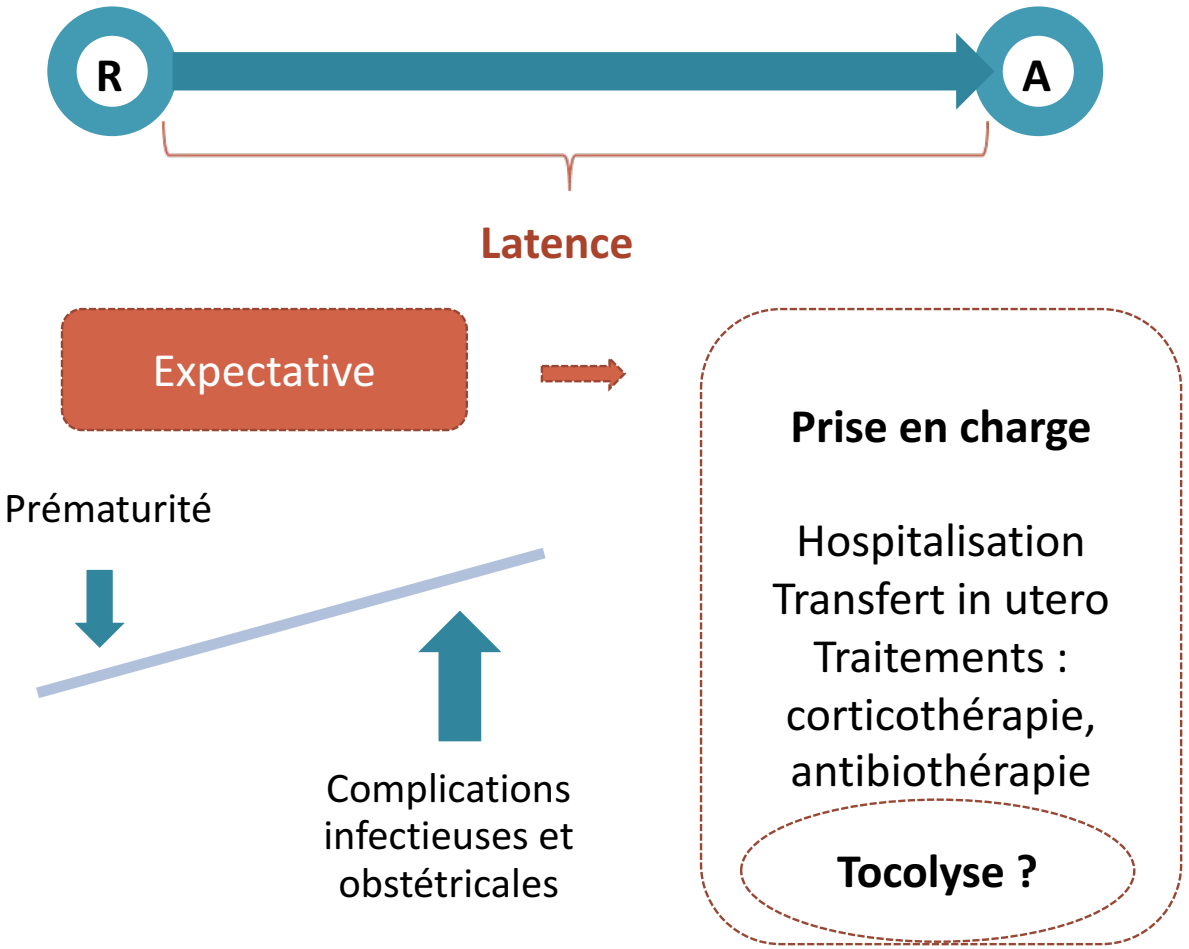
Rupture prématurée des membranes avant terme (RPMAT)

Rupture spontanée des membranes, survenant avant 37 SA et avant le début du travail

3% des grossesses, 30% des accouchements prématurés



CNGOF 1999, Mercer 2003, Roberts 2006, Goldenberg 2008, Kenyon 2013, Mackeen 2014, ACOG 2016

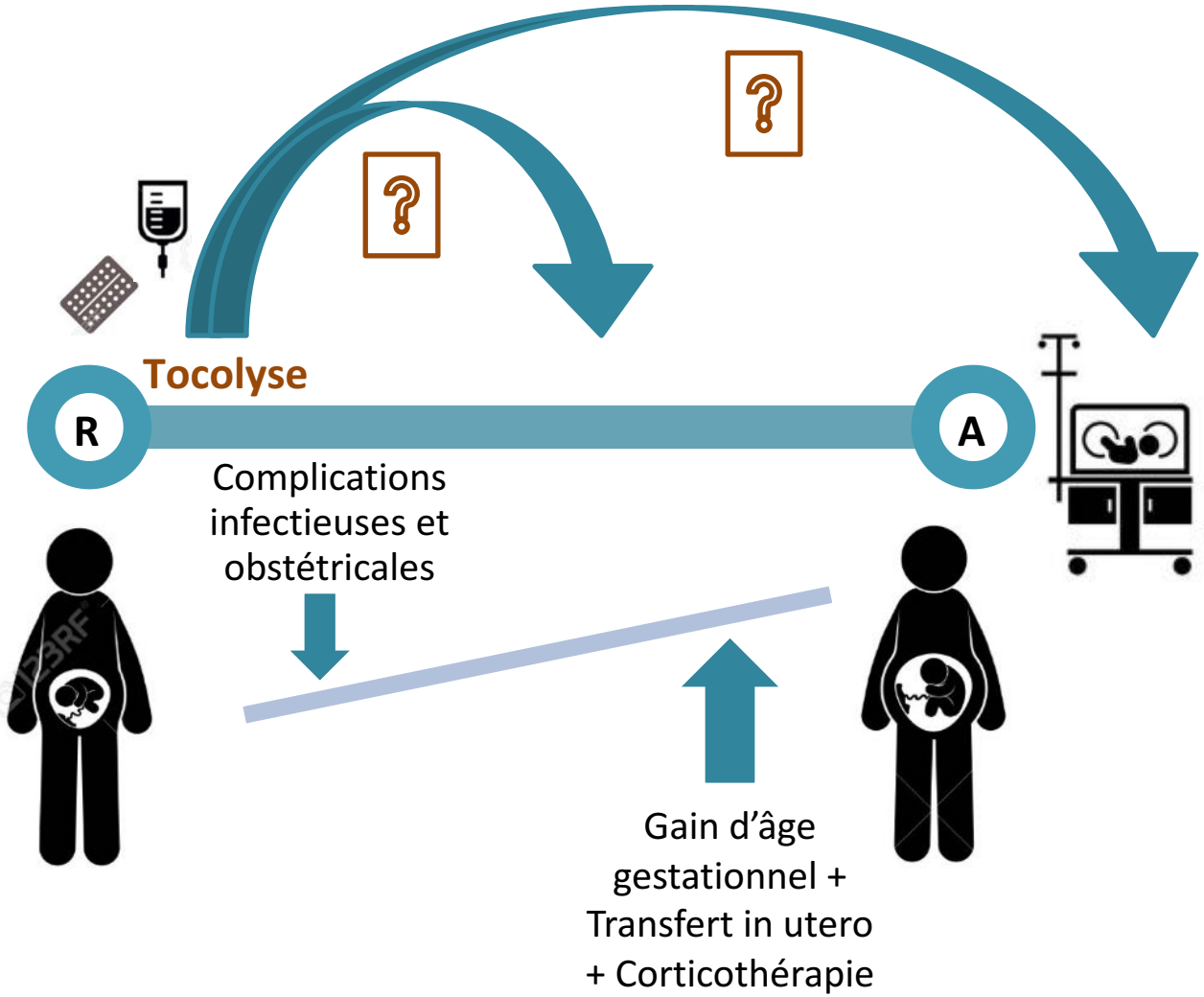
Tocolyse après RPMAT ?

- Littérature : méta-analyse de 2014, 8 essais, 408 patientes
  - Pas de données probantes pour recommander la tocolyse après RPMAT : ↗ durée de latence sans bénéfice néonatal, ↗ chorioamniotite
  - Limites : essais anciens, petits effectifs, prise en charge différente
- Recommandations internationales contrastées
- En pratique : tocolyse administrée après RPMAT dans 30 à 60% des cas

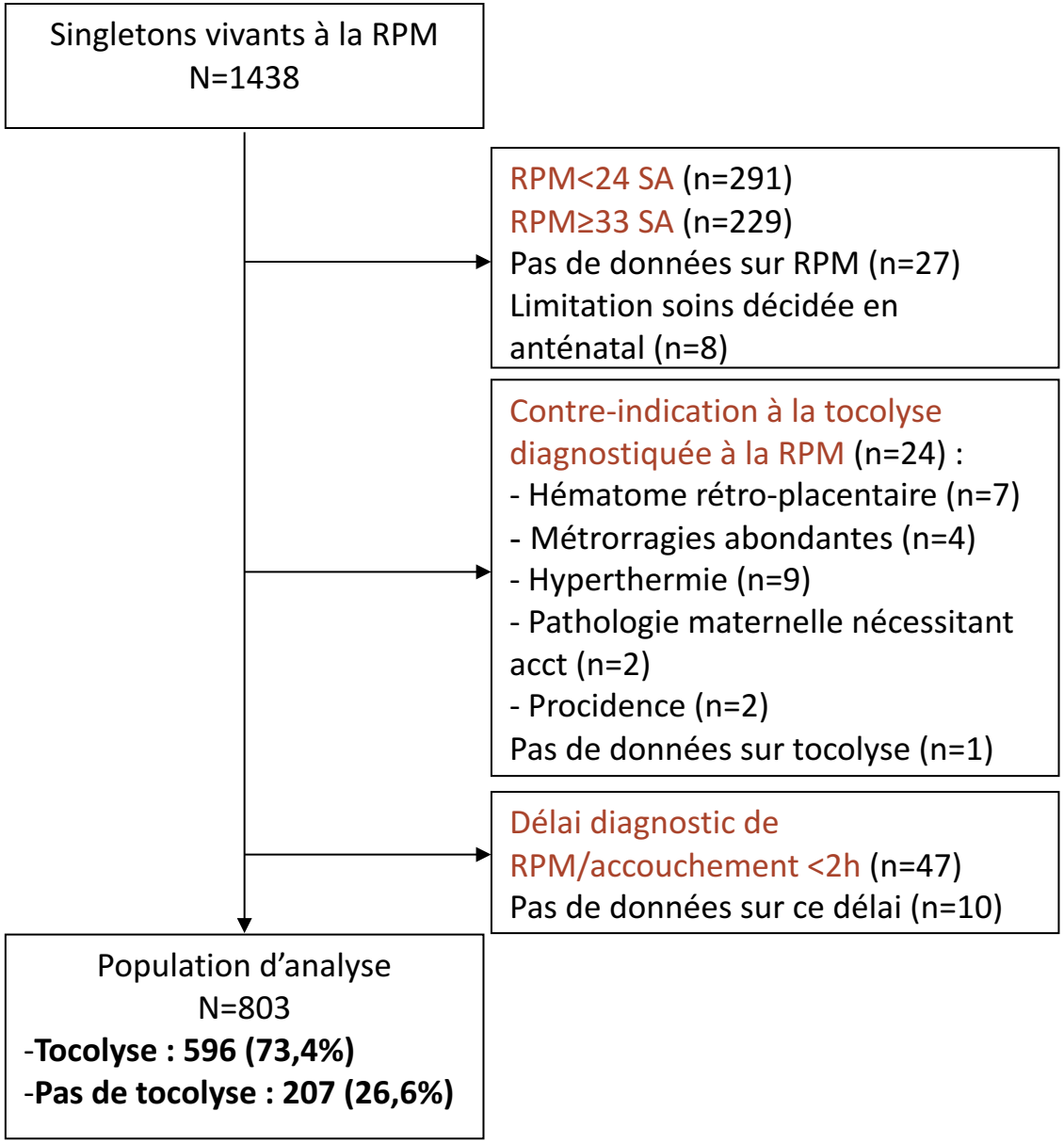
CNGOF 1999, Ramsey 2004, Fox 2008, Couteau 2013, Mackeen 2014, RCOG 2016, ACOG 2016

Objectif

Evaluer l'impact de l'administration d'une tocolyse après RPMAT sur les issues obstétricales et néonatales.



Population d'étude

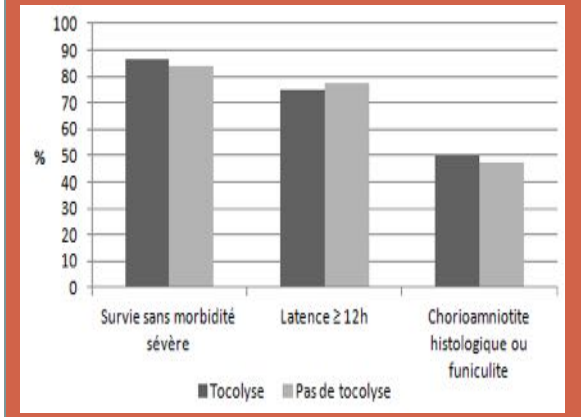


Analyse statistique

- Comparaison des caractéristiques selon le groupe de tocolyse
- Biais d'indication
- Création d'un score de propension (SP)
  - Pondération inverse du SP (IPTW)
- Critères de jugement
  - Survie sans morbidité sévère
  - Durée de latence ≥ 48h
  - Chorioamniotite histologique ou funiculite
- Analyses de sensibilité
  - RPMAT 26-31 SA
  - Latence ≥ 12 heures
- Données manquantes
  - Imputation multiple

Résultats

Issues selon l'administration d'une tocolyse



Association entre l'administration d'une tocolyse après RPMAT et les issues obstétricales et néonatales

	Population totale	RPMAT à 26-31 SA	Latence ≥ 12h
	OR (IC 95%)	OR (IC 95%)	OR (IC 95%)
Survie sans morbidité sévère	(n=803)	(n=549)	(n=686)
Pas de tocolyse	Ref	Ref	Ref
Tocolyse	1.01 (0.94-1.09)	1.06 (0.98-1.15)	1.01 (0.93-1.10)
Durée de latence ≥ 48h	(n=803)	(n=549)	(n=686)
Pas de tocolyse	Ref	Ref	Ref
Tocolyse	1.03 (0.95-1.11)	1.04 (0.95-1.14)	1.05 (0.97-1.13)
Chorioamniotite histologique ou funiculite	(n=494)*	(n=323)*	(n=429)*
Pas de tocolyse	Ref	Ref	Ref
Tocolyse	1.03 (0.92-1.17)	1.03 (0.88-1.19)	1.05 (0.92-1.20)

* Analyse restreinte aux histologies placentaires réalisées.

Discussion

- Forces
  - Cohérence des différentes analyses
  - Large population proche de la réalité clinique et des pratiques actuelles
  - Critère de jugement principal = pronostic néonatal
- Limites
  - Données observationnelles → score de propension
  - Troncature à droite ≥35SA → restriction aux RPMAT<33SA
- Conclusion
  - Pas de bénéfice néonatal ou obstétrical
  - Peu de différence entre les groupes : traitement inefficace?
  - Effets secondaires potentiels
  - Pas d'argument pour recommander ce traitement

Perspectives : essai TOCOPROM

Investigateur principal : Gilles Kayem

Responsable scientifique et coordinatrice : Elsa Lorthe

Méthodologiste : Pierre-Yves Ancel

Financement :

PHRC-N 2016 (1,2 M€)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

- Essai randomisé contrôlé en double aveugle : Nifedipine vs placebo pendant 48h en cas de RPMAT entre $22^{0/7}$ et $33^{6/7}$SA
- Critères de jugement
  - Principal : morti-morbidité périnatale
  - Secondaires : prolongation de la grossesse, morbidité néonatale mineure, morbidité maternelle
- Inclusions
  - N=850
  - 28 centres
  - 3,5 ans (à partir de janvier 2019)

Merci

- EPIPAGE2 : la coordination nationale, les responsables scientifiques, les coordinateurs régionaux, les cliniciens, les familles et les enfants, le groupe obstétrique
- Equipe EPOPé, INSERM U1153
- ED 393
- Contrat doctoral de l'UPMC

Tocolyse :

Variables incluses dans le SP :

- AG à la RPMAT, moment de la RPMAT (avant/pendant hospitalisation), transfert in utero, contractions à l'admission,
- Caractéristiques maternelles (pays, âge),
- Prise en charge obstétricale (type de centre, corticothérapie, antibiothérapie),
- Caractéristiques fœtales (sexe, présentation, zscore du poids de naissance <3^{e} percentile)

TABLE 1
Maternal, obstetric, and center characteristics without and with tocolysis administration after preterm premature rupture of membranes

Characteristics	No tocolysis (n = 207)	Tocolysis (n = 596)	*P* value
Maternal characteristics			
Age, y, median (IQR) (n = 802)	30 (26–39)	29 (26–33)	.11
Born in France or Europe (n = 786)	149 (75.9)	463 (78.7)	.56
Married (n = 787)	173 (89.9)	521 (90.5)	.83
Primiparity (n = 797)	98 (48.4)	280 (51.9)	.54
Obstetric characteristics and management			
PPROM before hospitalization (n = 803)	155 (81.3)	515 (88.3)	.04
Contractions at admission (n = 759)	71 (33.0)	249 (44.1)	.05
Gestational age at PPROM, WG (n = 803), median (IQR)	30 (27–32)	30 (27–31)	.83
Latency duration, d, median (IQR) (n = 787)	6 (2.0–12.0)	5 (1.9–11.5)	.26
Gestational age at birth, WG (n = 803), median (IQR)	31 (29–33)	31 (29–32)	.99
In utero transfer (n = 803)	72 (27.4)	415 (63.3)	< .001
Antibiotics (n = 803)	193 (95.8)	579 (97.0)	.43
Antenatal steroids (n = 803)	179 (89.0)	552 (89.0)	.99
Magnesium sulfate (n = 787)	10 (3.2)	34 (4.0)	.53
Type of labor (n = 801)			.002
Spontaneous labor	101 (42.4)	357 (61.4)	
Induction of labor	25 (18.9)	32 (8.1)	
Cesarean delivery before labor	80 (38.7)	206 (30.5)	

TABLE 1

Maternal, obstetric, and center characteristics without and with tocolysis administration after preterm premature rupture of membranes

Characteristics	No tocolysis (n = 207)	Tocolysis (n = 596)	*P* value
Mode of delivery (n = 798)			.11
Vaginal delivery	94 (44.2)	300 (55.9)	
Cesarean delivery before labor	80 (38.8)	206 (30.6)	
Cesarean delivery during labor	31 (17.0)	87 (13.5)	
Cephalic presentation (n = 785)	134 (73.7)	413 (72.4)	.79
Male fetus (n = 803)	116 (57.9)	325 (54.3)	.51
Birthweight ≤third percentile of the normalized z-score (n = 802)	18 (8.4)	35 (5.4)	.26
Clinical chorioamnionitis (n = 792)	16 (4.7)	40 (5.6)	.59
Maternity unit characteristics			
Type of maternity unit (n = 803)			.30
Type 1 (no neonatal department)	2 (2.0)	4 (0.4)	
Type 2 (with neonatal department)	30 (20.6)	56 (23.2)	
Type 3 (with neonatal intensive care department)	175 (77.4)	536 (76.4)	

Data are n (percentage) unless indicated. Percentages are weighted by recruitment period. The 2 groups were compared by a Mann-Whitney *U* test for medians and a χ^2 or Fisher exact test for categorical variables.

IQR, interquartile range; *PPROM*, preterm premature rupture of membranes; *WG*, weeks gestation.

Lorthe et al. Tocolysis after PPROM and neonatal outcome. Am J Obstet Gynecol 2017.

TABLE 2

Survival without severe morbidity, latency prolonged by ≥48 hours and histological chorioamnionitis without and with tocolysis administration after PPROM

Outcome GA at PPROM, wks	Total n/N, %	No tocolysis n/N, %	Tocolysis n/N, %	*P* value
Survival without severe morbidity	619/785 (85.9[a])	156/207 (83.9[a])	463/596 (86.7[a])	.39
24–26	150/262 (62.4)	36/67 (56.3)	114/195 (64.3)	.26
27–29	226/258 (89.0)	57/63 (92.1)	169/195 (88.0)	.35
30–32	243/265 (93.5)	63/73 (89.2)	180/192 (95.2)	.14
Latency prolonged by ≥48 h	597/803 (75.7[a])	147/207 (77.4[a])	450/596 (75.1[a])	.59
24–26	220/272 (83.6)	52/69 (76.9)	168/203 (85.7)	.09
27–29	215/262 (84.1)	49/64 (80.4)	166/198 (85.4)	.35
30–32	162/269 (68.4)	46/74 (76.2)	116/195 (65.4)	.15
Histological chorioamnionitis or funisitis	280/494[b] (49.5[a])	66/120 (47.6[a])	214/374 (50.0[a])	.73
24–26	130/198 (63.9)	33/49 (68.2)	97/149 (62.6)	.50
27–29	96/162 (56.3)	20/35 (57.1)	76/127 (56.1)	.92
30–32	54/134 (37.0)	13/36 (32.8)	41/98 (38.5)	.65

The 2 groups were compared by the χ^2 or Fisher exact test.

GA, gestational age; *PPROM*, preterm premature rupture of membranes.

[a] Percentages are weighted by recruitment period; [b] Among the histological examinations carried out.

Lorthe et al. Tocolysis after PPROM and neonatal outcome. Am J Obstet Gynecol 2017.

TABLE 3

Association between tocolysis administration after PPROM and survival without severe morbidity, latency prolonged by ≥48 hours and histological chorioamnionitis after inverse probability of treatment weighting

Outcome	Whole population OR (95% CI)	PPROM at 26–31 WG OR (95% CI)	Latency ≥12 h OR (95% CI)
Survival without severe morbidity[a]	(n = 803)[b]	(n = 549)[b]	(n = 686)[b]
No tocolysis	Reference	Reference	Reference
Tocolysis	1.01 (0.94–1.09)	1.06 (0.98–1.15)	1.01 (0.93–1.10)
Latency prolonged by ≥48 h[c]	(n = 803)[b]	(n = 549)[b]	(n = 686)[b]
No tocolysis	Reference	Reference	Reference
Tocolysis	1.03 (0.95–1.11)	1.04 (0.95–1.14)	1.05 (0.97–1.13)
Histological chorioamnionitis or funisitis[d]	(n = 494)[e]	(n = 323)[e]	(n = 429)[e]
No tocolysis	Reference	Reference	Reference
Tocolysis	1.03 (0.92–1.17)	1.03 (0.88–1.19)	1.05 (0.92–1.20)

CI, confidence interval; *OR*, odds ratio; *PPROM*, preterm premature rupture of membranes; *WG*, weeks gestation.

[a] Covariates used to estimate the propensity score: type of maternity unit, country of mother's birth, maternal age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, in utero transfer, antenatal steroids, antibiotics, fetal sex, presentation, and birthweight less than the third percentile of the normalized z-score; [b] Obtained after multiple imputations; [c] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, in utero transfer, antenatal steroids, antibiotics, fetal sex, presentation, and birthweight less than the third percentile of the normalized z-score; [d] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, in utero transfer, antenatal steroids, antibiotics, and presentation; [e] For performed placental examination.

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APPENDIX TABLE 1

Detailed neonatal outcomes without and with tocolysis administration

Outcome GA at PPROM, wks	Total n/N, %[a]	No tocolysis n/N, %[a]	Tocolysis n/N, %[a]	*P* value
Survival at discharge	718/803 (93.9)	182/207 (93.4)	536/596 (94.2)	.62
24–26	202/272 (77.4)	48/69 (71.2)	154/203 (79.3)	.16
27–29	249/262 (95.6)	61/64 (96.1)	188/198 (95.4)	.81
30–32	267/269 (99.7)	73/74 (99.4)	194/195 (99.8)	.50
Early-onset sepsis[b]	31/766 (3.4)	9/193 (4.4)	22/573 (3.0)	.49
24–26	10/242 (3.7)	2/57 (3.2)	8/185 (3.8)	.82
27–29	11/259 (5.2)	4/64 (5.2)	7/195 (5.2)	.99
30–32	10/265 (2.4)	3/72 (4.3)	7/193 (1.6)	.23
Severe cerebral lesion[c,d]	32/717 (3.5)	11/182 (4.8)	21/535 (3.0)	.34
24–26	15/202 (6.3)	6/48 (11.2)	9/154 (5.0)	.11
27–29	8/248 (2.8)	3/61 (4.1)	5/187 (2.4)	.47
30–32	9/267 (2.9)	2/73 (3.7)	7/194 (2.6)	.72
Severe bronchopulmonary dysplasia[c]	30/699 (2.4)	4/177 (1.3)	26/522 (2.8)	.13
24–26	21/190 (9.2)	3/45 (6.6)	18/145 (9.9)	.51
27–29	7/246 (2.5)	0/60 (0.0)	7/186 (3.4)	.13
30–32	2/263 (0.3)	1/72 (0.6)	1/191 (0.2)	.50
Necrotizing enterocolitis[c]	16/716 (2.2)	6/182 (3.5)	10/534 (1.8)	.32
24–26	4/200 (1.9)	1/48 (1.9)	3/152 (1.9)	.98
27–29	4/249 (1.4)	0/61 (0.0)	4/188 (1.9)	.24
30–32	8/267 (2.7)	5/73 (5.4)	3/194 (1.7)	.19
Retinopathy of prematurity[c]	7/718 (0.5)	2/182 (0.7)	5/536 (0.5)	.63
24–26	6/202 (2.6)	1/48 (2.5)	5/154 (2.6)	.99
27–29	0/246 (0.0)	0/61 (0.0)	0/188 (0.0)	—
30–32	1/267 (0.2)	1/73 (0.6)	0/194 (0.0)	.11

GA, gestational age; *PPROM*, preterm premature rupture of membranes.

[a] Percentages are weighted by recruitment period; [b] Among infants transfered to a neonatal intensive care unit; [c] Among infants alive at discharge; [d] Severe cerebral lesion include grade III intraventricular hemorrhage, intraparenchymal hemorrhage, or cystic periventricular leukomalacia.

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APPENDIX TABLE 2

Association between the initial tocolytic drug after PPROM and survival without severe morbidity, latency prolonged by ≥48 hours, and histological chorioamnionitis after inverse probability of treatment weighting

Outcome	Oxytocin receptor antagonists OR (95% CI)	Calcium-channel blockers OR (95% CI)
Survival without severe morbidity[a]	(n = 474)[b]	(n = 494)[b]
No tocolysis	Reference	Reference
Tocolysis	1.01 (0.92–1.11)	1.03 (0.96–1.11)
Latency prolonged by ≥48 h[c]	(n = 474)[b]	(n = 494)[b]
No tocolysis	Reference	Reference
Tocolysis	0.97 (0.88–1.07)	1.06 (0.97–1.14)
Histological chorioamnionitis or funisitis[e]	(n = 289)[d]	(n = 297)[d]
No tocolysis	Reference	Reference
Tocolysis	1.06 (0.92–1.23)	1.05 (0.93–1.18)

CI, confidence interval; *OR*, odds ratio; *PPROM*, preterm premature rupture of membranes.

[a] Covariates used to estimate the propensity score: type of maternity unit, country of mother's birth, maternal age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, in utero transfer, antenatal steroids, antibiotics, fetal sex, presentation, and birthweight less than the third percentile of the normalized z-score; [b] Obtained after multiple imputations; [c] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, in utero transfer, antenatal steroids, antibiotics, fetal sex, presentation, and birthweight less than the third percentile of the normalized z-score; [d] For performed placental examination; [e] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, in utero transfer, antenatal steroids, antibiotics, and presentation.

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APPENDIX TABLE 3

Association between tocolysis administration after PPROM and survival without severe morbidity, latency prolonged by ≥48 hours, and histological chorioamnionitis in women admitted directly after PPROM with and without contractions

Outcome	With uterine contractions at admission OR (95% CI)	Without uterine contractions at admission OR (95% CI)
Survival without severe morbidity[a]	(n = 115)[b]	(n = 135)[b]
No tocolysis	Reference	Reference
Tocolysis	1.10 (0.95–1.27)	1.08 (0.96–1.22)
Latency prolonged by ≥48 h[c]	(n = 115)[b]	(n = 135)[b]
No tocolysis	Reference	Reference
Tocolysis	1.15 (0.97–1.37)	1.04 (0.92–1.17)
Histological chorioamnionitis or funisitis[d]	(n = 67)[e]	(n = 79)[e]
No tocolysis	Reference	Reference
Tocolysis	1.00 (0.76–1.30)	1.07 (0.88–1.30)

CI, confidence interval; *OR*, odds ratio; *PPROM*, preterm premature rupture of membranes.

[a] Covariates used to estimate the propensity score: type of maternity unit, country of mother's birth, maternal age, gestational age at PPROM, antenatal steroids, antibiotics, fetal sex, presentation, birthweight less than the third percentile of the normalized z-score; [b] Obtained after multiple imputations; [c] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, antenatal steroids, antibiotics, fetal sex, presentation, and birthweight less than the third percentile of the normalized z-score; [d] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, antenatal steroids, antibiotics, and presentation; [e] For performed placental examination.

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