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OBSTETRICS

Tocolysis after preterm prelabor rupture of membranes and 5-year outcomes: a population-based cohort study



Elsa Lorthe, RM, PhD; Laetitia Marchand-Martin, MSc; Mathilde Letouzey, MD, PhD; Adrien M. Aubert, PhD; Véronique Pierrat, MD, PhD; Valérie Benhammou, PhD; Pierre Delorme, MD, PhD; Stéphane Marret, MD, PhD; Pierre-Yves Ancel, MD, PhD; François Goffinet, MD, PhD; Laurence Foix L'Hélias, MD, PhD; Gilles Kayem, MD, PhD; On behalf of the EPIPAGE-2 Obstetric Writing Group

BACKGROUND: The administration of tocolytics after preterm prelabor rupture of membranes remains a controversial practice. In theory, reducing uterine contractility should delay delivery and allow for optimal antenatal management, thereby reducing the risks for prematurity and adverse consequences over the life course. However, tocolysis may be associated with neonatal death or long-term adverse neurodevelopmental outcomes, mainly related to prolonged fetal exposure to intrauterine infection or inflammation. In a previous study, we showed that tocolysis administration was not associated with short-term benefits. There are currently no data available to evaluate the impact of tocolysis on neurodevelopmental outcomes in school-aged children born prematurely in this clinical setting.

OBJECTIVE: This study aimed to investigate whether tocolysis administered after preterm prelabor rupture of membranes is associated with neurodevelopmental outcomes at 5.5 years of age.

STUDY DESIGN: We used data from a prospective, population-based cohort study of preterm births recruited in 2011 (referred to as the EPIPAGE-2 study) and for whom the results of a comprehensive medical and neurodevelopmental assessment of the infant at age 5.5 years were available. We included pregnant individuals with preterm prelabor rupture of membranes at 24 to 32 weeks' gestation in singleton pregnancies with a live fetus at the time of rupture, birth at 24 to 34 weeks' gestation, and participation of the infant in an assessment at 5.5 years of age. Exposure was the administration of any tocolytic treatment after preterm prelabor rupture of membranes. The main outcome was survival without moderate to severe neurodevelopmental disabilities at 5.5 years of age. Secondary

outcomes included survival without any neurodevelopmental disabilities, cerebral palsy, full-scale intelligence quotient, developmental coordination disorders, and behavioral difficulties. A propensity-score analysis was used to minimize the indication bias in the estimation of the treatment effect on outcomes.

RESULTS: Overall, 596 of 803 pregnant individuals (73.4%) received tocolytics after preterm prelabor rupture of membranes. At the 5.5-year follow-up, 82.7% and 82.5% of the children in the tocolysis and no tocolysis groups, respectively, were alive without moderate to severe neurodevelopmental disabilities; 52.7% and 51.1%, respectively, were alive without any neurodevelopmental disabilities. After applying multiple imputations and inverse probability of treatment weighting, we found no association between the exposure to tocolytics and survival without moderate to severe neurodevelopmental disabilities (odds ratio, 0.93; 95% confidence interval, 0.55–1.60), survival without any neurodevelopmental disabilities (odds ratio, 1.02; 95% confidence interval, 0.65–1.61), or any of the other outcomes.

CONCLUSION: There was no difference in the neurodevelopmental outcomes at age 5.5 years among children with and without antenatal exposure to tocolysis after preterm prelabor rupture of membranes. To date, the health benefits of tocolytics remain unproven, both in the short- and long-term.

Key words: EPIPAGE-2, neurodevelopment, neurodevelopmental disabilities, obstetrical intervention, preterm children, preterm prelabor rupture of membranes, propensity score, school age, tocolysis

Introduction

Preterm prelabor rupture of membranes (PPROM) complicates 3% of pregnancies and accounts for one-third of preterm births.^{1–3} It is a leading cause of

neonatal mortality and morbidity and increases the risk for maternal infectious morbidity.^{2,4} Currently, expectant management is recommended before 34 weeks' gestation in the absence of labor, chorioamnionitis, or fetal distress.^{5–8} However, the use of a short-course of tocolytics after PPRM remains controversial,⁴ because no data with a sufficient level of evidence is available to recommend or advise against it.^{6,7,9}

In theory, reducing uterine contractility should delay delivery and allow for optimal antenatal management, including in utero transfer if necessary, corticosteroids, and antibiotics.⁴ This approach aims to reduce the risks of prematurity and adverse consequences

over the life course.¹⁰ In contrast, tocolytics may have a direct effect on the fetal brain^{11–13} or an indirect effect related to prolonged fetal exposure to intrauterine infection or inflammation.^{14–19} It may also impart a higher risk for neonatal sepsis^{15,20} that is potentially associated with neonatal death or long-term adverse neurodevelopmental outcomes.^{18,21,22} Neurodevelopment at school age is of particular interest to parents and medical and educational teams in this clinical setting given the aforementioned pathophysiological processes that contribute to adverse outcomes in neonates and beyond.²³

The optimal treatment strategy should be defined by taking both short- and long-

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AJOG at a Glance

Why was this study conducted?

There are currently no data to properly assess the impact of tocolysis on the neurodevelopmental outcomes of school-aged children born prematurely after preterm prelabor rupture of membranes (PPROM).

Key findings

Most pregnant individuals with PPRM who delivered prematurely received tocolytics. There were no differences in the neurodevelopmental outcomes at age 5.5 years among children with and without antenatal exposure to tocolytics after PPRM.

What does this add to what is known?

Our findings provide reassurance about the safety of tocolytic administration but also question its use because no health improvement was evidenced. These results complement and extend previous research, which showed that administering tocolytics after PPRM did not translate into improved short-term obstetrical or neonatal outcomes. To date, its health benefits remain unproven, both in the short- and long-term.

term outcomes into account. There is currently no evidence to suggest that the administration of tocolytics improves short-term neonatal outcomes.^{4,24,25} Only a few clinical studies have evaluated the impact of tocolysis after PPRM beyond the neonatal period.^{26–30} None have yielded robust conclusions, because they investigated outdated treatment strategies (eg, maintenance tocolysis),^{27,28} compared two tocolytic treatments,^{28–30} had very limited sample sizes (usually less than 100),^{27,30} or co-included pregnant individuals with preterm labor and intact membranes.^{28,29} In addition, these studies had follow-up periods that were limited to early childhood (2 years of age)^{27,28} or covering a wide age range.²⁹ The World Health Organization has classified this gap in knowledge as a high priority research question related to tocolytic treatments.⁹

Therefore, building upon a large cohort of preterm infants and previous research focusing on neonatal and obstetrical outcomes,²⁴ we aimed to investigate if the administration of tocolytics after PPRM was associated with neurodevelopmental outcomes at 5.5 years of age.

Materials and Methods**Study design and setting**

Briefly, EPIPAGE-2 is a prospective, population-based birth cohort of

extremely, very, and moderately preterm infants, that aimed to estimate the short- and long-term outcomes and their association with individual characteristics and unit practices.³¹ All births (terminations of pregnancy, stillbirths, and live births) from 22^{0/7} to 34^{6/7} weeks' gestation that occurred in all 546 maternity units of the 25 of 26 regions in France in 2011 were eligible. Recruitment was conducted over 3 distinct periods based on gestational age at birth, namely an 8-month recruitment period for births at 22 to 26 weeks' gestation, a 6-month period for births at 27 to 31 weeks' gestation, and a 5-week period for births at 32 to 34 weeks' gestation. A total of 7804 newborns were included at baseline (participation rate, 93%). Of those, 4312 were eligible for follow-up. Maternal, obstetrical, and neonatal data were collected from medical records following a standardized protocol.

All survivors were invited to participate in a comprehensive neurodevelopmental assessment at age 5.5 years, along with a sample of 600 term born children from the French Longitudinal Study since Childhood (ELFE) cohort³² intended to serve as a reference for developmental tests.³³ Parents completed a self-administered questionnaire, whereas children had a clinical examination by a physician and a

cognitive assessment by a neuropsychologist that were both performed in dedicated examination centers with specifically trained professionals to ensure homogeneity in data collection. At 5.5 years, at least 1 assessment was performed for 3083 (78%) children. Full details of the cohort recruitment and data collection were previously reported elsewhere.^{31,33}

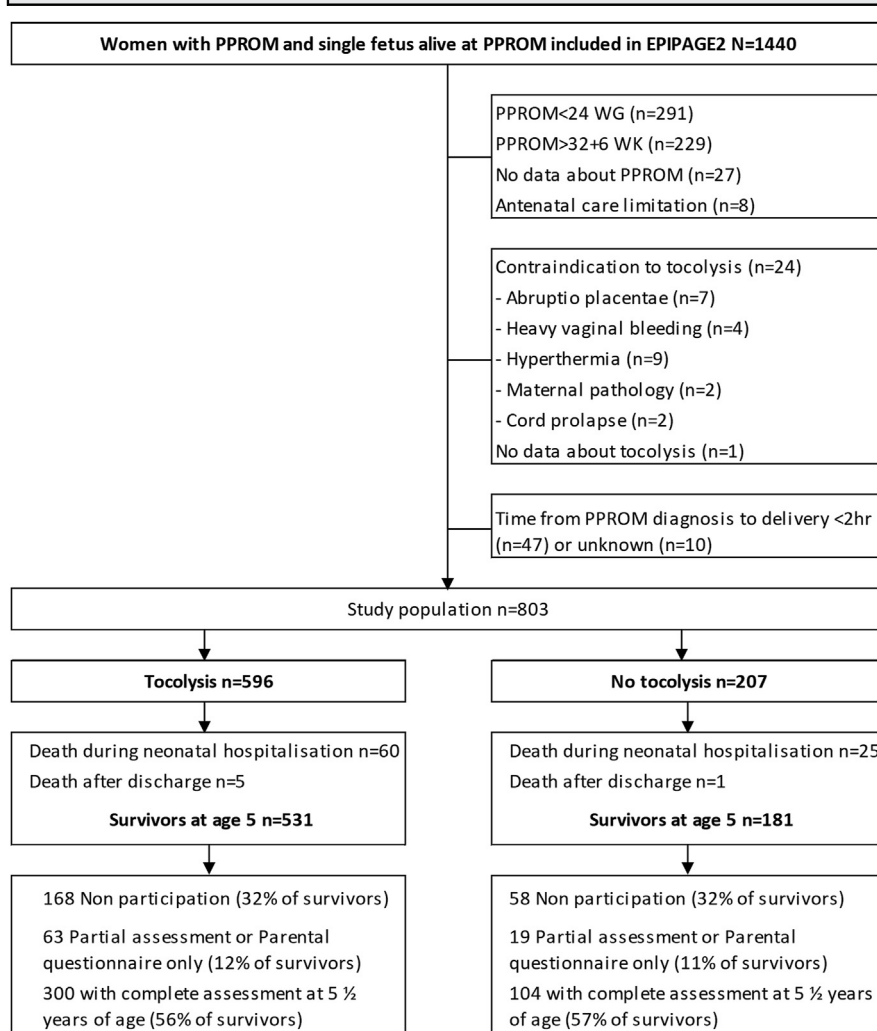
Ethical approval

Assessments occurred only after families had received information and provided written informed consent. This study was approved by the National Data Protection Authority (CNIL DR-2016-290) and by the appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, reference No 16.263; Committee for the Protection of People Participating in Biomedical Research, reference 2016-A00333-48).

Study population

We included the exact same sample as in our previous publication²⁴ with the eligibility criteria being PPRM occurring at 24^{0/7} to 32^{6/7} weeks' gestation in viable singleton pregnancies with a live fetus at the time of PPRM and birth at 24^{0/7} to 34^{6/7} weeks' gestation. PPRM was defined as spontaneous rupture of membranes before admission to the delivery room and diagnosed at least 2 hours before birth. As recommended, the diagnosis was based on maternal history and a sterile speculum examination with a diagnostic test performed if necessary. A further inclusion criterion was participation in the assessment at 5.5 years of age.

Pregnant individuals with multiples pregnancies (n=2020), terminations of pregnancies (n=1292), home births (n=54), fetal death before maternal admission to the hospital (n=675), lethal malformations (n=103), and precursor to delivery other than PPRM (n=2220) were excluded. Finally, we excluded all women with any contraindications to tocolysis or with care limitations because of an antenatal diagnosis of poor prognosis (Figure 1).

FIGURE 1
Flow chart

PPROM, preterm prelabor rupture of membranes.

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Exposure and outcome measures

The exposure was the administration of any tocolytic treatment after PPROM diagnosis (classified as tocolysis vs no tocolysis). The first-line tocolytics used in France were atosiban and nifedipine.

The primary composite outcome was survival without moderate to severe neurodevelopmental disabilities at 5.5 years.³³ Survival was defined as the number of children alive at 5.5 years relative to the number of fetuses alive at the time of PPROM. We defined severe neurodevelopmental disabilities as severe cerebral palsy (Gross Motor Function Classification System [GMFCS] 4 or

5), bilateral binocular visual acuity < 1/10 and/or uni- or bilateral hearing loss > 70 dB and/or Full-Scale Intelligence Quotient (FSIQ) score of < -3 standard deviations (SDs) from the mean (Wechsler Preschool and Primary Scale of Intelligence, 4th edition). Moderate neurodevelopmental disabilities included cerebral palsy with a GMFCS score of 2 or 3, bilateral binocular visual acuity $\geq 1/10$ and < 3.2/10 and/or uni- or bilateral hearing loss of 40 to 70 dB and/or FSIQ between -3 to -2 SDs from the mean. Mild neurodevelopmental disabilities were defined as mild cerebral palsy (GMFCS score of 1), visual disability

$\geq 3.2/10$ and < 5/10 and/or uni- or bilateral hearing loss < 40 dB and/or FSIQ score between -2 and -1 SDs from the mean and/or developmental coordination disorders (Movement Assessment Battery for Children, 2nd edition [MABC-2], total score ≤ 5 th percentile), and/or behavioral difficulties (Strengths and Difficulties Questionnaire [SDQ], total score ≥ 90 th percentile). All cutoffs were those of the distribution related to the reference group born at term.³³ We also assessed survival without any neurodevelopmental disabilities as a secondary outcome and all the aforementioned criteria taken separately.

Other variables

We considered the following variables in the analysis: sociodemographic characteristics (maternal age, country of birth, education, parental socioeconomic position—which was added to this analysis because of its strong impact on childhood outcomes), clinical factors (parity, uterine contractions at admission, gestational age at PPROM, PPROM before hospitalization), fetal characteristics (sex, presentation, and birthweight \leq third percentile), and obstetrical management (in utero transfer, administration of antenatal steroids or antibiotics, type of maternity unit). Uterine contractions were identified based on tracings of uterine activity recorded at admission. Gestational age was estimated based on the best obstetrical estimate, which combined information from the last menstrual period and the first trimester ultrasonography assessment. Administration of antenatal steroids was categorized as receiving at least 1 injection vs no injection. Babies were considered small for gestational age if their birth weight was \leq third percentile of the French intrauterine growth curves adjusted for sex and gestational age.³⁴ Socioeconomic position was defined by the highest occupational position between the occupations of the parents or of the mother only if living alone.

Statistical analysis

Maternal and child characteristics and outcomes were described as frequencies and percentages in each group (with and

without tocolysis). Percentages were weighted according to the duration of the recruitment periods (in weeks) for each gestational age group; weights were 1.0 (35/35) for births at 24 to 26 weeks' gestation, 1.34 (35/26) for births at 27 to 31 weeks' gestation, and 7.0 (35/5) for births at 32 to 34 weeks' gestation. Weighting allowed us to account for the sampling scheme of the cohort and to ensure representativeness.

We compared the characteristics of the children with an incomplete assessment (n=82) and no assessment (n=226) at 5.5 years with those of children with a complete follow-up evaluation. Categorical variables were compared using chi-square or Fisher exact tests as appropriate.

We used a propensity-score analysis intended to minimize the indication bias when estimating the treatment effect.³⁵ The propensity score was defined as the pregnant individual's probability of receiving tocolysis based on their characteristics at baseline (excluding covariates that may be affected by the treatment, such as gestational age at birth), namely all the aforementioned sociodemographic characteristics, clinical factors, obstetrical management, and fetal characteristics. We then applied inverse probability of treatment weighting (IPTW) based on the estimated propensity scores to obtain 2 groups with balanced observed baseline covariates (as confirmed by postweighting standardized differences all <10%) (Supplemental Figure), which only differed by treatment allocation. The association between tocolysis and each outcome was estimated using a logistic regression model within the weighted sample, obtaining odds ratios (ORs) and 95% confidence intervals (CIs) with robust standard errors.

The proportion of missing data for baseline characteristics ranged from 0% to 17.9% for each covariate but exceeded 5.0% only for contractions at admission (5.5%), socioeconomic status (6.5%), and maternal level of education (17.9%). Overall, the primary outcome was missing for 43.3%. Complete case analysis for the composite survival outcomes may undermine the representativeness

of the estimates and introduce selection biases. The main results were therefore presented after multiple imputations to account for selective dropouts and missing information at follow-up. Missing baseline and outcome variables were handled by multiple imputations by chained equations with the SAS multiple imputation procedure (SAS Institute, Cary, NC).³⁶ Considering missing data as missing at random based on the variables included in the imputation model, we generated 50 independent imputed data sets with 20 iterations each by using all the baseline and outcome variables and those potentially predicting attrition and/or outcomes. A propensity score analysis was performed in each imputed data set to estimate the exposure effect, and estimates were pooled according to Rubin's rules.

We performed the following sensitivity analyses. First, we presented the results of the analyses of complete cases with restriction to children with a follow-up at 5.5 years. Second, we reported a greedy matching on the propensity score, performed using the PSMATCH SAS procedure without replacement within a caliper of 0.2 SDs of the logit of the propensity score. Each exposed infant was matched to the closest non-exposed infant, leading to matching 202 children exposed to tocolytics with 202 non-exposed children. This procedure estimated the average treatment effect on the treated (ATT). Third, we investigated the association between the initial tocolytic drug administered (oxytocin receptor antagonists, calcium channel blockers, no tocolysis) and the outcomes by applying a 3-group propensity score based on a generalized boosted modeling to calculate the average treatment effect (ATE) weights for optimal balance between the 3 groups using the `mnp`s function in the `twang` statistical package in R (R Core Team, Vienna, Austria).³⁷ Fourth, considering French clinical practices in 2011, antenatal management may have differed for the earliest gestational age group, leading to poorer outcomes. We therefore replicated our analyses in a subgroup of participants with PPRM at 26 to 31 weeks' gestation. Fifth, we also

applied a stricter definition of PPRM (ie, latency ≥ 12 hours), which is commonly reported in the literature² and excludes women with membranes ruptured during labor. Finally, we tried to disentangle the efficacy of tocolytics among pregnant individuals with and without contractions by replicating the analyses in these 2 subgroups of patients.

Statistical analyses were performed using SAS, version 9.4, and R, version 4.0.2.

Results

A total of 803 pregnant individuals were included in our previous analysis that focused on perinatal outcomes among whom 596 (weighted percentage, 73.4%) received tocolytics after PPRM and 207 (weighted percentage, 26.6%) did not (Figure 1). Among 712 children alive at 5.5 years, 300 of 531 (56.5%) in the tocolysis group and 104 of 181 (57.5%) in the no tocolysis group had a complete follow-up assessment, whereas 63 of 531 (11.9%) and 19 of 181 (10.5%) in the respective groups had a partial assessment. Children lost to follow-up had younger mothers, with a lower education level, and lower socioeconomic positions than those with a complete assessment (Supplemental Table 1). However, there were no differences in clinical management across these groups, including tocolytic administration.

Baseline sociodemographic and clinical characteristics by exposure to tocolysis are reported in Table 1. Tocolytics were more frequently administered to women with uterine contractions and in utero transfer. All baseline covariates were well-balanced after creating propensity scores and applying IPTW (Supplemental Figure).

At the 5.5-year follow-up, 82.7% and 82.5% of children in the tocolysis and no tocolysis groups, respectively, were alive without moderate to severe neurodevelopmental disabilities; 52.7% and 51.1% in the respective groups were alive without any disabilities (Table 2). The frequency of all other outcomes by exposure group is detailed in Table 2 and Supplemental Table 2. After applying multiple imputations and IPTW, we found no association between exposure

TABLE 1
Baseline characteristics according to exposure to tocolysis

Characteristics	Tocolysis (n=596)		No tocolysis (n=207)	
	n	% ^a	n	% ^a
Maternal characteristics				
Age (y) (n=803)				
<25 y	33	4.7	8	2.4
25–34 y	469	80.8	158	78.1
≥35 y	94	14.5	41	19.5
Nulliparity (n=786)	280	51.9	98	48.4
Born in France or Europe (n=786)	463	78.7	149	75.9
Level of education (n=659)				
Less than high school	164	31.6	57	36.4
High school, 1–2 y of graduate studies	217	43.9	65	38.4
≥3 y of graduate studies	121	24.4	35	25.2
Parents' socioeconomic position^b (n=751)				
Executive	119	20.2	39	19.7
Intermediate	87	16.4	21	10.2
Administration	167	30.9	70	40.5
Service, trade	83	16.5	25	14.5
Worker, unemployed	108	16.0	32	15.1
Obstetrical characteristics and management				
PPROM before hospitalization (n=803)	515	88.3	155	81.3
Contractions at admission (n=759)	249	44.1	71	33.0
Gestational age at PPRM (wk) (n=803), median (IQR)	30 (27–31)		30 (27–32)	
24	56	6.4	25	6.5
25	89	8.7	28	7.5
26	58	6.8	16	4.4
27	58	6.9	25	9.6
28	65	8.8	17	7.0
29	75	10.5	22	8.6
30	81	12.2	29	11.0
31	76	16.1	27	14.5
32	38	23.6	18	30.9
In utero transfer (n=803)	415	63.3	72	27.4
Antibiotics (n=803)	579	97.0	193	95.8
Antenatal steroids (n=803)	552	89.0	179	89.0
Neonatal characteristics				
Cephalic presentation (n=785)	413	72.4	134	73.7
Male fetus (n=803)	325	54.3	116	57.9
Birth weight ≤third percentile (n=802)	35	5.4	18	8.4

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(continued)

TABLE 1
Baseline characteristics according to exposure to tocolysis (continued)

Characteristics	Tocolysis (n=596)		No tocolysis (n=207)	
Maternity unit characteristics				
Type of maternity unit (n=803)				
Type 1 (no neonatal department)	4	0.4	2	2.0
Type 2 (with neonatal department)	56	23.2	30	20.6
Type 3 (with neonatal intensive care department)	536	76.4	175	77.4

The data for n=803 participants are presented.

IQR, interquartile range; PPRM, preterm prelabor rupture of membranes; SD, standardized difference.

^a Denominators vary according to the number of missing data for each variable. Percentages are weighted to take into account the differences in survey design between gestational age groups, thus proportions are not exact number of events or number in groups because of the weighting; ^b Defined as the highest occupational status between occupations of the mother and the father or mother only if living alone.

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to tocolysis and survival without moderate to severe neurodevelopmental disabilities (OR, 0.93; 95% CI, 0.55–1.60), survival without any neurodevelopmental disabilities (OR, 1.02; 95% CI, 0.65–1.61), or any of the other outcomes (Table 2). Similar results were obtained after complete cases analyses, matching on the propensity score, and in all subgroup analyses (Figure 2, Figure 3, Supplemental Table 3). The frequency of survival without moderate to severe neurodevelopmental disabilities was 80.7% and 83.7% after antenatal exposure to oxytocin receptor antagonists and calcium channel blockers, respectively (Supplemental Table 2). Once again, there was no association between the initial tocolytic treatment and any of the neurodevelopmental outcomes under investigation (Supplemental Table 3).

Comment

Principal findings

We found no differences in the neurodevelopmental outcomes at age 5.5 years among children with and without antenatal exposure to tocolytics after PPRM. These results complement and extend previous research, which showed that administering tocolytics after PPRM did not translate into improved short-term obstetrical or neonatal outcomes.

Strengths and limitations

Our study was based on a large, prospective, population-based sample of

participants exposed to PPRM at a national level and detailed high-quality data. Furthermore, obstetrical management was consistent with the current clinical guidelines, particular in terms of antenatal administration of steroids and antibiotics, thereby ensuring that our findings accurately reflect routine clinical practice. The follow-up at 5.5 years of age included both parental insights and a standardized medical and neuropsychological evaluation conducted by trained professionals, further enhancing the reliability and validity of our results. Given the dearth of evidence-based data regarding school-age outcomes after antenatal exposure to pregnancy complications and treatments, such observational studies provide valuable insights for evaluating routine clinical practices in a real-life setting.

The findings should be interpreted in light of the study's limitations. Loss to follow-up and selection bias are inherently associated with any long-term follow-up of cohort participants.³³ If this sample is representative of the preterm population in terms of neonatal characteristics, attrition over time was relatively high and socially determined as classically reported in longitudinal cohort studies.^{31,33,38} Social factors, such as a low socioeconomic position, are known to be associated with both loss to follow-up and poor long-term outcomes.³³ Therefore, the proportion of children with suboptimal neurodevelopmental outcomes is likely

underestimated in our study sample and in complete-cases analyses which is why we presented the main results after multiple imputations. Treatment allocation was not randomized in this observational study. We therefore performed analyses that minimized indication bias as much as possible. By design, babies born after 34^{6/7} weeks' gestation were not included in the EPIPAGE-2 cohort. We restricted our analyses to cases of PPRM before 33 weeks' gestation and likely missed a small proportion of PPRM cases that occurred before 33 weeks' gestation with delivery after 34^{6/7} weeks, that is, those with the longest latency durations and the best prognoses.

Results in the context of what is known

Although most women with PPRM who delivered prematurely received tocolytics, the treatment was not associated with either prolonged gestation by ≥ 48 hours, neonatal outcomes,²⁴ or neurodevelopment at 5.5 years of age. Together with our previous article, we think that this study makes an important contribution to our understanding of the short- and long-term consequences of administering tocolytics after PPRM.

Very few observational studies and randomized trials have examined the benefits and harms of tocolysis in women with PPRM and their children.^{4,25,27–30,39} Most had limited external validity and reliability and

TABLE 2

Association between tocolysis and 5-year outcomes, after multiple imputation and inverse probability treatment weighting

Outcome	Tocolysis	No tocolysis	After inverse probability of treatment weighting	
	% ^a n=596	% ^a n=207	OR or MD (95% CI)	P value
Survival without moderate to severe neurodevelopmental disabilities at 5.5 y ^b	82.7	82.5	0.93 (0.55–1.60)	.56
Survival without any neurodevelopmental disabilities at 5.5 y ^b	52.7	51.1	1.02 (0.65–1.61)	.62
Survival at 5.5 y	93.2	93.1	0.78 (0.43–1.42)	.41
Among survivors at 5.5 y	n=531	n=181		
Neurodevelopmental disabilities ^b				
Severe	1.6	2.5	0.68 (0.17–2.71)	.65
Moderate	9.6	8.9	1.00 (0.53–1.85)	
Mild	38.2	42.2	0.94 (0.66–1.32)	
None	50.6	46.4	Ref	
Cerebral palsy	4.6	8.6	0.86 (0.36–2.02)	.60
FSIQ score				
Mean (SD)	97.1 (13.6)	97.0 (13.5)	1.1 (–2.5 to 4.7)	.38
<79 (<–2 SD) ^c	8.2	8.1	1.06 (0.42–2.71)	.51
Behavioral difficulties				
Total SDQ score, mean (SD)	10.8 (5.3)	11.2 (5.1)	–0.0 (–1.2 to 1.1)	.63
Total SDQ score ≥90th percentile ^c	9.5	9.7	1.31 (0.53–3.21)	.45
Developmental Coordination Disorders ^d				
Total MABC-2 score, mean (SD)	10.5 (3.1)	9.7 (2.9)	0.7 (–0.1 to 1.5)	.11
Total MABC-2 score ≤5th percentile ^c	6.4	7.7	0.65 (0.26–1.61)	.32

CI, confidence interval; dB, decibels; FSIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System; MABC-2, Movement Assessment Battery for Children - Second Edition (Henderson, 2007); MD, mean difference; OR, odd ratios; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire (Goodman, 1997).

^a Weighted to take into account the differences in survey design between gestational age groups; ^b Severe neurodevelopmental disabilities were defined as severe cerebral palsy (GMFCS score of 4 or 5) and/or bilateral binocular visual acuity <1/10 and/or uni- or bilateral hearing loss >70 dB and/or FSIQ score <–3 SDs. Moderate neurodevelopmental disabilities were defined as cerebral palsy with a GMFCS score of 2 or 3 and/or bilateral binocular visual acuity ≥1/10 and <3.2/10 and/or uni- or bilateral hearing loss at 40 to 70 dB and/or FSIQ score between –3 to –2 SDs. Mild neurodevelopmental disabilities were defined as mild cerebral palsy (GMFCS score of 1) and/or visual disability ≥3.2/10 and <5/10 and/or uni- or bilateral hearing loss at <40 dB and/or FSIQ score between –2 and –1 SDs and/or MABC-2 score ≤5th percentile and/or SDQ score ≥90th percentile. Cutoffs of the distribution was related to a reference group born at term; ^c Cutoff of the distribution related to a reference group born at term; ^d Among children without cerebral palsy, severe or moderate sensory disabilities, and with Full-Scale Intelligence Quotient score ≥2 SDs.

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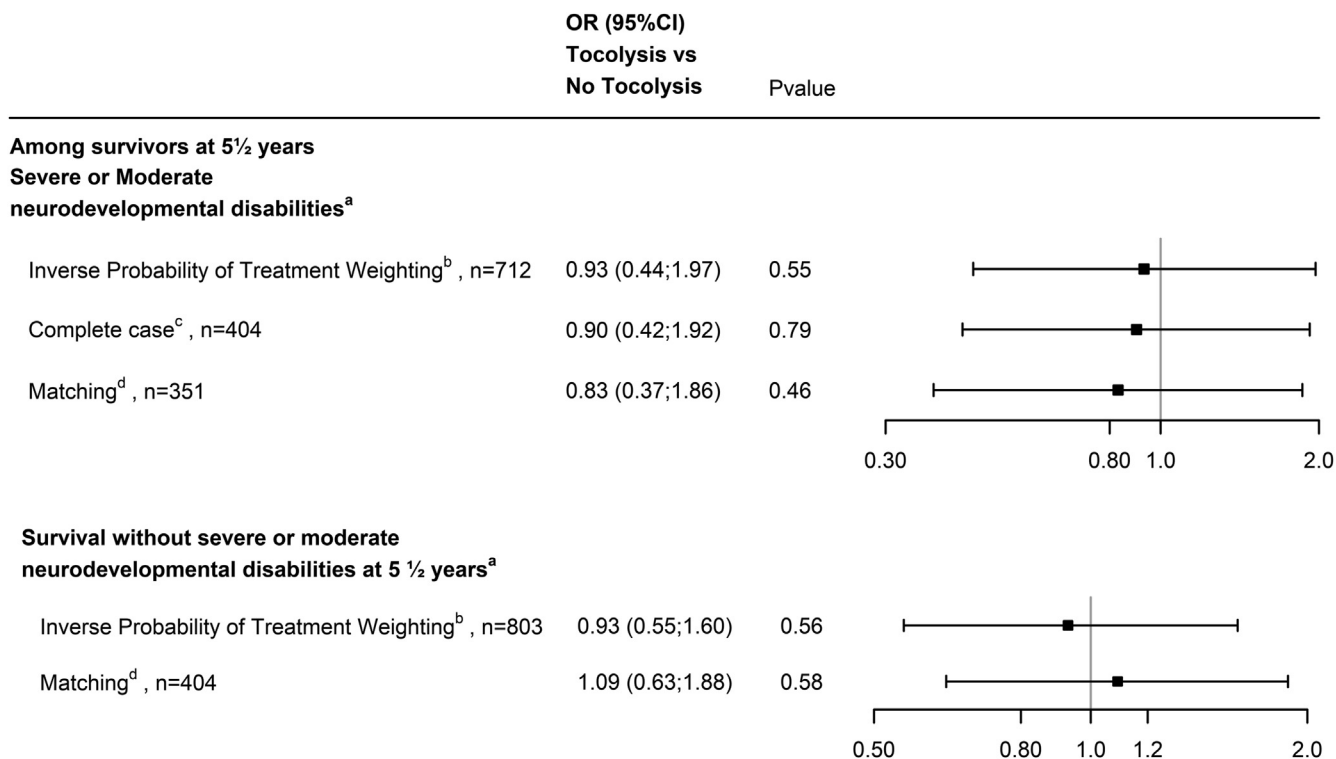
almost none reported long-term outcomes. Briefly, the 2-year follow-up in the Assessment of Perinatal Outcome after Sustained Tocolysis in Early Labor II (APOSTEL II) trial (maintenance tocolysis with nifedipine vs placebo after threatened preterm labor) focused on maintenance tocolysis, which is not recommended.²⁷ Furthermore, this study was largely underpowered to show any differences in outcomes (n=46 women with PPROM). Similarly, another study

reported the 2-year follow-up of a small sample of children exposed to nifedipine vs ritodrine for 7 days.²⁸ The proportion of women with PPROM was not reported, and a non-validated parental questionnaire was used to assess developmental outcomes. Children born to participants in the APOSTEL III trial (tocolysis with nifedipine vs atosiban after threatened preterm labor) were followed once over a wide age range (2.5 to 5.5 years of age).²⁹ No results were

reported specifically for the small subgroup of children born after PPROM. The only long-term follow-up study (9–12 years) of children exposed in utero to tocolytics compared behavioral-emotional outcomes, quality of life, motor function, parenting distress, and education of children exposed to nifedipine with those exposed to ritodrine.³⁰ No significant differences in the long-term outcomes were observed, but fewer than 100 children were evaluated.

FIGURE 2

Association between tocolysis and 5-year outcomes: sensitivity analyses



Superscript letter a denotes severe neurodevelopmental disabilities were defined as severe cerebral palsy (GMFCS score of 4 or 5) and/or bilateral binocular visual acuity <1/10 and/or uni- or bilateral hearing loss at >70 dB and/or FSIQ score <−3 SDs. Moderate neurodevelopmental disabilities were defined cerebral palsy with a GMFCS score of 2 or 3 and/or bilateral binocular visual acuity ≥1/10 and <3.2/10 and/or uni- or bilateral hearing loss at 40 to 70 dB and/or FSIQ score between −3 to −2 SDs. Mild neurodevelopmental disabilities were defined as mild cerebral palsy (GMFCS score of 1) and/or visual disability ≥3.2/10 and <5/10 and/or uni- or bilateral hearing loss at <40 dB, and/or FSIQ score between −2 and −1 SDs and/or MADC-2 score ≤5th percentile and/or SDQ score ≥90th percentile. Cutoffs of the distribution were compared with a reference group born at term; *Superscript letter b* denotes main analysis, inverse probability of treatment weighting with multiple imputation of missing data; *Superscript letter c* denotes inverse probability of treatment weighting only for children with complete neurodevelopmental evaluation at 5.5 years and included n=104 infants exposed to tocolysis and n=300 not exposed to tocolysis; *Superscript letter d* denotes a total of 202 exposed infants (of which 177 survived to 5 years) were matched to 202 nonexposed infants (of which 174 survived to 5 years).

CI, confidence interval; dB, decibel; FSIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System; MADC-2, Movement Assessment Battery for Children-Second Edition; OR, odds ratio; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire.

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Clinical implications

On a positive note, we found no evidence of adverse long-term outcomes associated with tocolytic administration. There is indeed a body of evidence that has linked exposure to obstetrical infections or antenatal inflammation to the activation of innate immune cells in the fetal brain, which contributes to abnormal oligodendrocyte and interneuron production and migration and to secondary demyelination and connectome dysfunction and may increase the risk for a spectrum

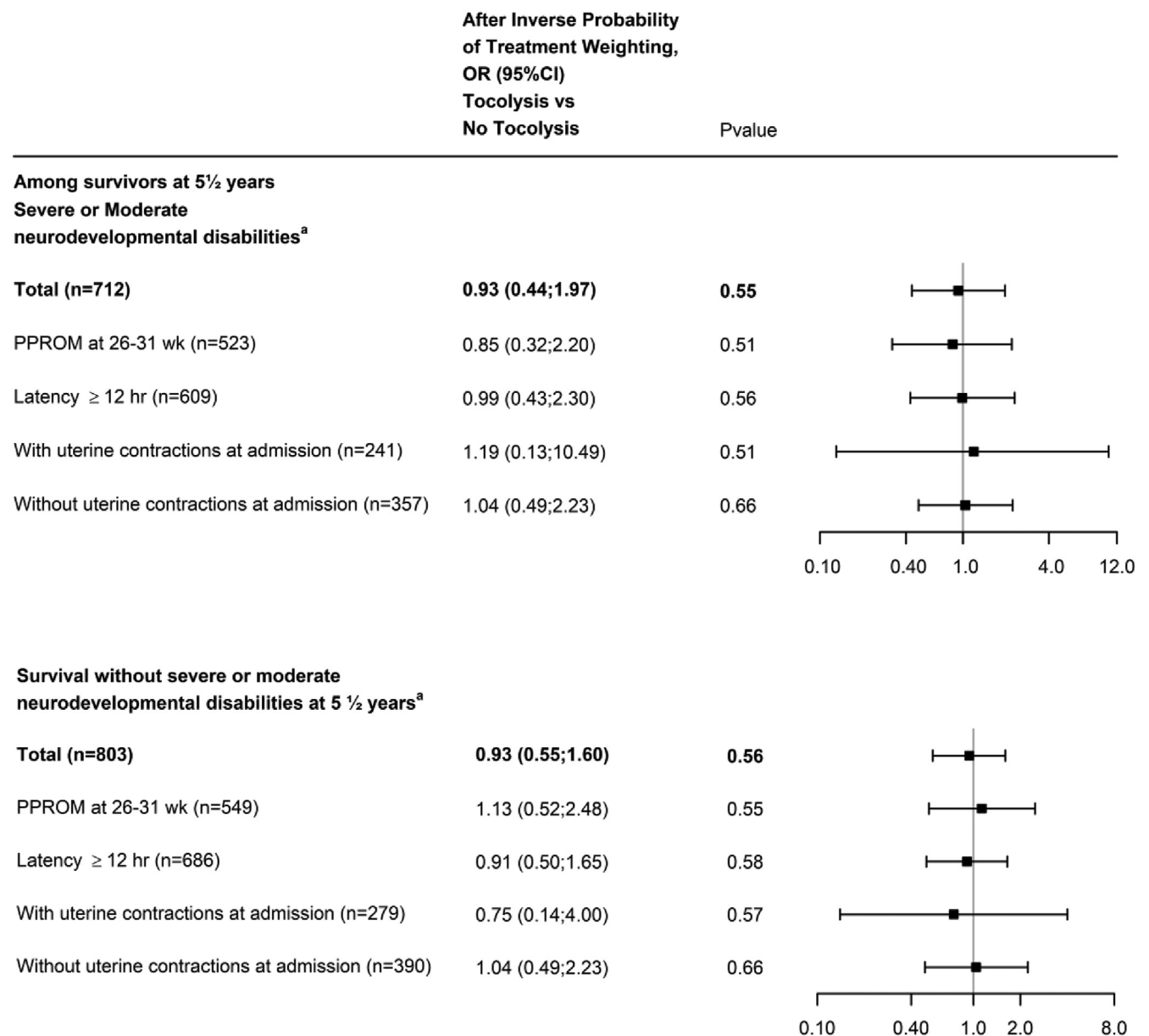
of neuropsychiatric disorders in children.¹⁸ This implies that the children's long-term development may be affected, even if an intervention is not associated with differences in short-term outcomes. The administration of diethylstilbestrol in the 1950s or, more recently, the administration of antibiotics for spontaneous preterm labor are prime examples of interventions that turned out to have important negative long-term effects.⁴⁰ Our findings provide some reassurance regarding the safety of tocolytic

administration in pregnant individuals with PPROM, although we cannot exclude differences in minor or mild neurodevelopmental outcomes or other important outcomes (eg, respiratory or digestive complications).

However, from a less positive perspective, it can be argued that we did not show any improvement in the neurodevelopment at school age, which is perhaps not surprising given the lack of benefits in terms of prolonging gestation or neonatal outcomes. Although our

FIGURE 3

Association between tocolysis and 5-year outcomes: subgroup analyses



Superscript letter *a* denotes severe neurodevelopmental disabilities were defined as severe cerebral palsy (GMFCS score of 4 or 5) and/or bilateral binocular visual acuity <1/10 and/or uni- or bilateral hearing loss at >70 dB and/or FSIQ score <−3 SDs. Moderate neurodevelopmental disabilities were defined cerebral palsy with a GMFCS score of 2 or 3 and/or bilateral binocular visual acuity ≥1/10 and <3.2/10 and/or uni- or bilateral hearing loss at 40 to 70 dB and/or FSIQ score between −3 to −2 SDs. Mild neurodevelopmental disabilities were defined as mild cerebral palsy (GMFCS score of 1) and/or visual disability ≥3.2/10 and <5/10 and/or uni- or bilateral hearing loss at <40 dB, and/or FSIQ score between −2 and −1 SDs and/or MADC-2 score ≤5th percentile and/or SDQ score ≥90th percentile. Cutoffs of the distribution were compared with a reference group born at term.

CI, confidence interval; dB, decibel; FSIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System; MABC-2, Movement Assessment Battery for Children- Second Edition; OR, odd ratios; PPRM, preterm prelabor rupture of membranes; SD, standard deviation; SDQ, Strengths and difficulties questionnaire.

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findings need replication, they further support that tocolysis may be an ineffective intervention in the setting of PPRM.⁴¹

Until further evidence is available, clinicians need to be aware of these findings when taking care of patients with PPRM and should consider that tocolysis may

provide more reassurance to medical teams, giving them the impression that they are taking action, than actual health benefits to patients.

Research implications

Tocolysis after PPRM is a paradoxical and controversial practice; there is no evidence of short-term neonatal benefits, but a large number of medical teams administer it routinely.⁴² This may be explained by the lack of reliable, up-to-date, and robust scientific evidence.³⁹ To better inform and tailor clinical practices and policies, we are conducting a randomized controlled trial aimed at assessing if 48-hour tocolysis by nifedipine reduces perinatal mortality or morbidity in PPRM at 22 to 33 weeks' gestation.³⁹ Follow-up evaluations at 2 and 6 years of age are planned. We hope that these efforts will advance scientific knowledge, permit optimization of antenatal management of pregnant individuals worldwide, and ultimately improve the prognosis for children born preterm after PPRM.

Conclusion

The administration of tocolytics after PPRM aims to improve neonatal outcomes and promote healthy development in later life, which should therefore be taken into account when defining the optimal treatment strategy for a pregnant individual. We showed no differences in the neurodevelopmental outcomes at 5.5 years of age among children with and without antenatal exposure to tocolytics after PPRM. To date, the health benefits of tocolysis remain unproven, both in the short- and in the long-term. ■

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Arthuis, MD, PhD (Department of Gynecology and Obstetrics, CIC, University hospital of Nantes, Nantes, France); Julie Blanc, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Department of Obstetrics and Gynecology, Aix Marseille University, Marseille, France); Pascal Boileau, MD, PhD (Department of Neonatal Pediatrics, Poissy Saint Germain Hospital, France, EA7285 Versailles Saint Quentin en Yvelines University, France); Thierry Debillon, MD, PhD (Department of Neonatal Pediatrics, University Hospital, Grenoble, France); Pierre Delorme, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Department of Obstetrics and Gynecology, Trousseau Hospital, AP-HP, Paris, France); Claude D'Ercole, MD (Department of Obstetrics and Gynecology, Nord Hospital, Assistance Publique des Hôpitaux de Marseille (AP-HM), Aix Marseille Université, AMU, Marseille, France); Thomas Desplanches, RM, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France); Caroline Diguisto, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Maternité Olympe de Gouges, University François Rabelais, Tours, France); Laurence Foix-L'Hélias, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Department of Neonatal Pediatrics, Trousseau Hospital, AP-HP, Paris, France); Géraldine Gascoin, MD, PhD (Department of Neonatal Medicine, University Hospital, Toulouse, France, Research Unit on Perinatal Epidemiology, Childhood Disabilities and Adolescent Health, Inserm UMR 1027, Paul Sabatier University, Toulouse, France); Catherine Gire, MD (Department of Neonatology, North Hospital, Marseille, France); François Goffinet, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Department of Obstetrics and Gynecology, Cochin, Hôtel Dieu Hospital, AP-HP, Paris, France); Isabelle Guellec, MD, PhD (Pediatric and Neonatal Intensive Care Unit, University Hospital, Nice, France, Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France); Gilles Kayem, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Sorbonne Universités, UPMC Univ Paris 06, IFD, 4 Place Jussieu, 75252 PARIS cedex 05, Paris, France, Department of Obstetrics and Gynecology, Trousseau Hospital, AP-HP, Paris, France); Bruno Langer, MD (Department of Obstetrics and Gynecology, Hautepierre Hospital, Strasbourg, France); Mathilde Letouzey, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Department of Neonatal Pediatrics,

Poissy Saint Germain Hospital, France); Elsa Lorthe, RM, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France); Emeline Maisonneuve, MD, MSc (Department of Obstetrics and Gynecology, Trousseau Hospital, APHP, Paris, France); Stéphane Marret, MD, PhD (Department of Neonatal Medicine, Rouen University Hospital and Région-Inserm (ERI 28), Normandy University, Rouen, France); Isabelle Monier, RM, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France); Andrei Morgan, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France); Jean-Christophe Rozé, MD, PhD (Department of Neonatal Medicine, Nantes University Hospital, Nantes, France, Epidémiologie Clinique, Centre d'Investigation Clinique (CIC004), Nantes University Hospital, Nantes, France); Thomas Schmitz, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Department of Obstetrics and Gynecology, Robert Debré Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France); Loïc Sentilhes, MD, PhD (Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France); Damien Subtil, MD, PhD (Department of Obstetrics and Gynecology, Jeanne de Flandre Hospital, Lille, France); Héloïse Torchin, MD, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France, Neonatal Medicine and Resuscitation Service, Port-Royal, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France); Barthélémy Tosello, MD, PhD (Department of Neonatology, Assistance Publique Hopitaux de Marseille, Marseille, France); Christophe Vaysière, MD, PhD (Department of Obstetrics and Gynecology, University Hospital, Toulouse, France, Research Unit on Perinatal Epidemiology, Childhood Disabilities and Adolescent Health, Inserm UMR 1027, Paul Sabatier University, Toulouse, France); Norbert Winer, MD, PhD (Department of Obstetrics and Gynecology, University Hospital, INRAE, UMR 1280 Physiologie des adaptations nutritionnelles, Nantes, France); Jennifer Zeitlin, PhD (Université Paris Cité, Epidemiology and Statistics Research Center/CRESS, Inserm, INRAE, F-75004 Paris, France).

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Author and article information

From the Unit of Population Epidemiology, Department of Primary Care Medicine, Geneva University Hospitals,

Geneva, Switzerland (Dr Lorthe); Université Paris Cité, Inserm, INRAE, Centre for Research in Epidemiology and Statistics (CRESS), Obstetrical Perinatal and Pediatric Epidemiology Research Team (EPOPé), Paris, France (Dr Lorthe, Ms Marchand-Martin, and Drs Letouzey, Aubert, Pierrat, Benhammou, Delorme, Ancel, Goffinet, Foix L'Hélias, and Kayem); Department of Neonatal Pediatrics, Poissy Saint Germain Hospital, Poissy, France (Dr Letouzey); Department of Neonatology, Centre Hospitalier Intercommunal Créteil, Créteil, France (Dr Pierrat); Department of Gynecology and Obstetrics, Armand Trousseau Hospital, APHP, FHU Prema, Paris Sorbonne University, Paris, France (Drs Delorme and Kayem); Department of Neonatal Pediatrics, Intensive Care, and Neuropediatrics, Rouen University Hospital, Rouen, France (Dr Marret); Inserm Unit 1245, Team Perinatal Handicap, School of Medicine of Rouen, Normandy

University, Normandy, France (Dr Marret); Clinical Research Unit, Center for Clinical Investigation P1419, Assistance Publique-Hôpitaux de Paris, Paris, France (Dr Ancel); AP-HP Centre, Maternité Port-Royal, Department of Obstetrics and Gynaecology, Université Paris Cité, FHU PREMA, Paris, France (Dr Goffinet); and Department of Neonatal Pediatrics, Armand Trousseau Hospital, APHP, FHU Prema, Paris Sorbonne University, Paris, France (Dr Foix L'Hélias).

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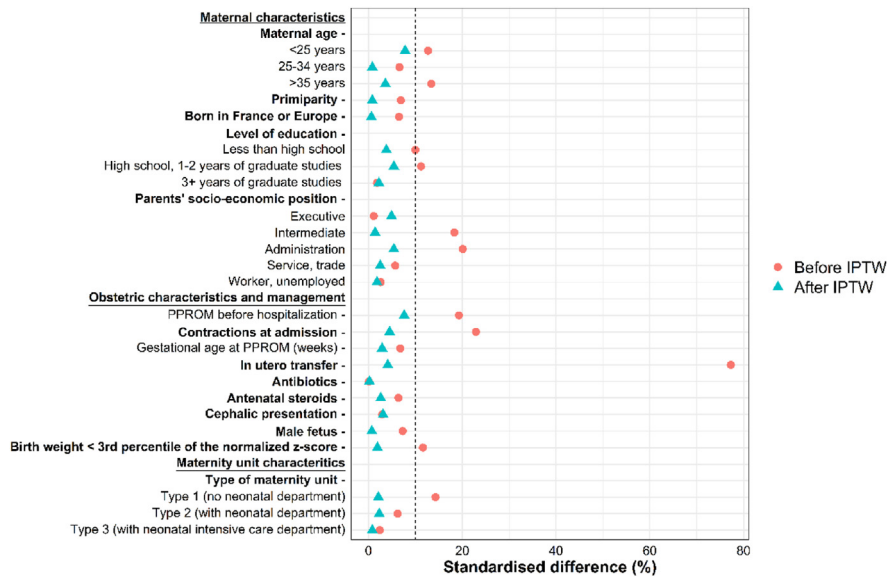
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Corresponding author: Elsa Lorthe, RM, PhD. elsa.lorthe@gmail.com

SUPPLEMENTAL FIGURE
Standardized differences for covariates used in the propensity score



Each point illustrates the standardized difference for each variable in the initial sample (red circles) and the propensity score IPTW model (blue triangle). The vertical line at 10% illustrates the standard cutoff for acceptable imbalance between groups.

IPTW, inverse probability of treatment weighting; *PPROM*, preterm prelabor rupture of membranes.

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SUPPLEMENTAL TABLE 1

Comparison of participating and nonparticipating children

Characteristics	Analysis population: children alive at 5½ y (n=712)						Chi-square P value
	Complete assessment (n=404)		Incomplete assessment ^a (n=82)		No assessment (n=226)		
	n/N ^b	% ^b	n/N ^b	% ^b	n/N ^b	% ^b	
Maternal characteristics							
Age (y)							
<25	14/404	2.1	3/82	2.9	18/226	7.5	.002
25–34	319/404	80.1	63/82	78.0	181/226	83.6	
≥35	71/404	17.8	16/82	19.2	27/226	8.9	
Nulliparity	195/401	53.9	34/82	43.3	108/224	49.9	.42
Born in France or Europe	321/398	80.2	69/81	89.1	154/222	71.1	.011
Level of education							
Less than high school	112/389	29.1	26/75	31.7	74/181	39.1	<.001
High school, 1–2 y of graduate studies	161/389	39.7	30/75	34.9	86/181	51.9	
≥3 y of graduate studies	116/389	31.2	19/75	33.5	21/181	9.0	
Parents' socioeconomic position^c							
Executive	107/386	27.1	20/78	27.6	20/207	6.0	<.001
Intermediate	62/386	16.8	15/78	18.4	20/207	10.3	
Administration	113/386	31.1	20/78	27.6	77/207	40.0	
Service, trade	56/386	14.2	10/78	9.7	32/207	20.8	
Worker, unemployed	48/386	10.8	13/78	16.7	58/207	22.9	
Obstetrical characteristics and management							
PPROM before hospitalization	348/404	88.8	64/81	84.5	186/226	85.4	.45
Contractions at admission	147/382	36.7	29/79	31.5	97/214	48.2	.047
Gestational age at PPRM (wk)							
24	24/404	4.8	4/82	2.9	20/226	4.6	.39
25	50/404	6.7	12/82	10.0	24/226	5.8	
26	40/404	6.6	5/82	4.3	18/226	4.7	
27	46/404	8.2	8/82	7.7	19/226	5.6	
28	50/404	9.5	13/82	12.5	17/226	6.2	
29	55/404	9.6	11/82	14.6	30/226	11.2	
30	54/404	11.5	17/82	20.4	37/226	12.0	
31	53/404	16.1	8/82	7.7	42/226	20.9	
32	32/404	27.0	4/82	20.0	19/226	28.9	
In utero transfer	242/404	50.7	58/82	65.1	136/226	56.2	.21
Antibiotics	389/404	97.0	78/82	96.4	218/226	96.5	.94
Antenatal steroids	373/404	90.4	78/82	92.4	204/226	86.3	.50
Tocolysis	300/404	72.3	63/82	83.6	168/226	86.3	.71
Neonatal characteristics							
Cephalic presentation	275/395	68.5	62/80	83.6	159/223	79.5	.004

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(continued)

SUPPLEMENTAL TABLE 1

Comparison of participating and nonparticipating children (continued)

Characteristics	Analysis population: children alive at 5½ y (n=712)						Chi-square P value
	Complete assessment (n=404)		Incomplete assessment ^a (n=82)		No assessment (n=226)		
	n/N ^b	% ^b	n/N ^b	% ^b	n/N ^b	% ^b	
Male fetus	237/404	61.0	36/82	41.4	116/226	48.2	.010
Birth weight ≤third percentile	19/404	5.7	7/82	6.7	16/226	5.8	.96
Maternity unit characteristics							
Type of maternity unit							
Type 1 (no neonatal department)	1/404	0.8	0/82	0	2/226	0.5	.75
Type 2 (with neonatal department)	43/404	22.0	9/82	20.7	25/226	25.7	
Type 3 (with neonatal intensive care department)	360/404	77.2	73/82	79.3	199/226	73.8	

PPROM, preterm premature rupture of membranes; SD, standardized difference.

^a Including 23 children with an incomplete neurodevelopmental assessment and 59 with only a postal questionnaire; ^b Denominators vary according to the number of missing data for each variable. Percentages are weighted to take into account the differences in survey design between gestational age groups, and thus proportions are not exactly the number of events or number in groups because of the weighting; ^c Defined as the highest occupational status between occupations of the mother and the father or of the mother only if living alone.

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SUPPLEMENTAL TABLE 2

Maternal, obstetrical, neonatal, and center characteristics according to tocolytic drug, after and before IPTW

Characteristics	Oxytocin receptor antagonists		Calcium channel blockers		No tocolysis		After inverse probability of treatment weighting ^a SD ^c
	(n=267)		(n=286)		(n=207)		
	n	% ^b	n	% ^b	n	% ^b	
Maternal characteristics							
Age (y)							
<25	15	5.5	17	4.7	8	2.4	8.0
25–34	214	82.9	219	77.8	158	78.1	5.5
≥35	38	11.6	50	17.6	41	19.5	10.5
Nulliparity	124	52.3	135	52.2	98	48.4	2.7
Born in France or Europe	231	91.3	200	68.3	149	75.9	0.7
Level of education							
Less than high school	72	30.4	78	32.4	57	36.4	3.4
High school, 1–2 y of graduate studies	97	45.6	104	40.5	65	38.4	0.1
≥3 y of graduate studies	53	24.0	64	27.1	35	25.2	4.0
Parents' socioeconomic status ^d							
Executive	48	18.1	65	22.3	39	19.7	6.6
Intermediate	41	17.8	39	16.1	21	10.2	1.5
Administration	79	35.1	78	26.5	70	40.5	4.3
Service, trade	37	12.0	43	20.6	25	14.5	1.7
Worker, unemployed	49	17.0	46	14.6	32	15.1	1.0
Obstetrical characteristics and management							
PPROM before hospitalization	232	88.3	240	86.8	155	81.3	6.0
Contractions at admission	122	45.1	112	45.2	71	33.0	5.1
Gestational age at PPRM (wk)							
24	22	6.5	29	5.3	25	6.5	13.5
25	43	10.5	40	7.5	28	7.5	1.3
26	29	7.7	24	5.0	16	4.4	0.0
27	24	7.1	28	6.4	25	9.6	0.2
28	34	12.6	26	5.9	17	7.0	0.8

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(continued)

SUPPLEMENTAL TABLE 2

Maternal, obstetrical, neonatal, and center characteristics according to tocolytic drug, after and before IPTW (continued)

Characteristics	Oxytocin receptor antagonists		Calcium channel blockers		No tocolysis		After inverse probability of treatment weighting ^a SD ^c
	(n=267)		(n=286)		(n=207)		
	n	% ^b	n	% ^b	n	% ^b	
29	37	13.5	34	8.7	22	8.6	9.9
30	34	11.4	40	12.0	29	11.0	2.7
31	32	12.0	41	20.8	27	14.5	2.0
32	12	18.6	24	28.4	18	30.9	11.9
In utero transfer	210	80.2	172	49.4	72	27.4	6.1
Antibiotics	248	86.9	263	90.3	179	89.0	7.6
Antenatal steroids	259	96.4	281	97.9	193	95.8	0.8
Neonatal characteristics							
Cephalic presentation	177	71.4	206	73.8	134	73.7	3.6
Male fetus	144	51.7	156	55.6	116	57.9	2.7
Birth weight ≤ third percentile	20	8.0	14	4.1	18	8.4	0.2
Maternity unit characteristics							
Type of maternity unit							
Type 1	2	0.6	2	0.3	2	2.0	6.6
Type 2 (with neonatal department)	22	16.6	31	29.0	30	20.6	6.5
Type 3 (with neonatal intensive care department)	243	82.8	253	70.7	175	77.4	4.6

PPROM, preterm premature rupture of membranes; SD, standardized difference.

^a After inverse probability of treatment weighting and multiple imputation for handling missing data; ^b Denominators vary according to the number of missing data for each variable. Percentages were weighted to take into account the differences in survey design between gestational age groups, and thus, proportions are not the exact number of events or number in groups because of the weighting; ^c Maximum standardized pairwise difference between the 3 groups; ^d Defined as the highest occupational status between occupations of the mother and the father or of the mother only if living alone.

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SUPPLEMENTAL TABLE 3
Neurodevelopmental outcomes according to tocolytic drug

Outcome	Oxytocin receptor antagonists % ^a	Calcium channel blockers % ^a	No tocolysis % ^a	After inverse probability of treatment weighting		P value
				OR or MD (95%CI)		
	n=267	n=286	n=207	Oxytocin receptor antagonists vs no tocolysis	Calcium channel blockers vs no tocolysis	
Survival without moderate to severe neurodevelopmental disabilities at 5.5 y ^b	80.7	83.7	82.5	1.03 (0.57–1.86)	0.92 (0.52–1.62)	.77
Survival without any disabilities at 5.5 y ^b	53.4	52.9	51.1	1.04 (0.61–1.76)	0.98 (0.61–1.58)	.82
Survival at 5.5 y	92.8	93.7	93.1	1.02 (0.53–1.96)	0.85 (0.45–1.62)	.80
Among survivors at 5.5 y	n=237	n=257	n=181			
Neurodevelopmental disabilities ^b						
Severe	1.8	1.5	2.5	0.69 (0.14–3.28)	0.80 (0.22–2.91)	.92
Moderate	11.2	9.1	8.9	1.06 (0.57–1.97)	1.05 (0.57–1.95)	
Mild	34.8	39.7	42.2	1.05 (0.72–1.52)	0.98 (0.69–1.39)	
None	52.1	49.7	46.4	Ref	Ref	
Cerebral palsy	6.2	3.9	8.6	0.91 (0.34–2.42)	0.96 (0.38–2.46)	.86
FSIQ score						
Mean (SD)	97.4 (13.5)	97 (13.9)	97 (13.5)	0.4 (–3.7 to 4.4)	0.9 (–2.8 to 4.7)	.68
<79 (<–2 SD) ^c	9.0	8.1	8.1	1.14 (0.41–3.14)	1.11 (0.41–2.99)	.79
Behavioral difficulties						
Total SDQ score, mean (SD)	10.5 (5.2)	11.0 (5.6)	11.2 (5.1)	0.2 (–1.3 to 1.6)	–0.0 (–1.3 to 1.2)	.82
Total SDQ score ≥90th percentile ^c	7.8	11.8	9.7	1.63 (0.58–4.57)	1.22 (0.47–3.14)	.05
Developmental Coordination Disorders ^d						
Total MABC-2 score, mean (SD)	10.2 (3.2)	10.7 (3)	9.7 (2.9)	0.0 (–1.0 to 1.1)	0.9 (–0.0 to 1.8)	.074
Total MABC-2 score ≤5th percentile ^c	7.5	6.0	7.7	1.10 (0.36–3.36)	0.57 (0.21–1.55)	.32

CI, confidence interval; dB, decibel; FSIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System (Ghassabian, 2016); MABC-2, Movement Assessment Battery for Children - Second Edition (Henderson, 2007); MD, mean difference; OR, odd ratios; SD, standard deviation; SDQ, Strengths and difficulties questionnaire (Goodman, 1997).

^a Weighted to take into account the differences in survey design between gestational age groups; ^b Severe neurodevelopmental disabilities were defined as severe cerebral palsy (GMFCS score of 4 or 5) and/or bilateral binocular visual acuity <1/10 and/or uni- or bilateral hearing loss >70 dB and/or FSIQ score <–3 SDs. Moderate neurodevelopmental disabilities were defined as cerebral palsy with a GMFCS score of 2 or 3 and/or bilateral binocular visual acuity ≥1/10 and <3.2/10 and/or uni- or bilateral hearing loss at 40 to 70 dB and/or FSIQ score between –3 to –2 SDs. Mild neurodevelopmental disabilities were defined as mild cerebral palsy (GMFCS score of 1) and/or visual disability ≥3.2/10 and <5/10 and/or uni- or bilateral hearing loss at <40 dB and/or FSIQ score between –2 and –1 SDs and/or MABC-2 score ≤5th percentile and/or SDQ score ≥90th percentile. Cutoffs of the distribution was related to a reference group born at term; ^c Cutoff of the distribution related to a reference group born at term; ^d Among children without cerebral palsy, severe or moderate sensory disabilities, and with Full-Scale Intelligence Quotient score ≥2 SDs.

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