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Condensation: Although frequently administered, tocolysis after preterm premature rupture of membranes is not associated with improved neonatal outcome, prolonged gestation or increased rate of histological chorioamnionitis.

Short title: Tocolysis after PPROM and neonatal outcome

Abstract

Background: There are conflicting results regarding tocolysis in cases of preterm premature rupture of membranes. Delaying delivery may reduce neonatal morbidity due to prematurity, allow for prenatal corticosteroids and, if necessary, *in utero* transfer. However, that may increase risks of maternofetal infection and its adverse consequences.

Objective: To investigate whether tocolytic therapy in cases of preterm premature rupture of membranes is associated with improved neonatal or obstetric outcomes.

Study design: EPIPAGE 2 is a French national prospective population-based cohort study of preterm births that occurred in 546 maternity units in 2011. Inclusion criteria in this analysis were women with preterm premature rupture of membranes at 24 to 32 weeks' gestation and singleton gestations. Outcomes were survival to discharge without severe morbidity, latency prolonged by ≥ 48 hours and histological chorioamnionitis. Uterine contractions at admission, individual and obstetric characteristics, and neonatal outcomes were compared by tocolytic treatment or not. Propensity scores and inverse probability of treatment weighting for each woman were used to minimize indication bias in estimating the association of tocolytic therapy with outcomes.

Results: The study population consisted of 803 women; 596 (73.4%) received tocolysis. Women with and without tocolysis did not differ in neonatal survival without severe morbidity (86.7% vs 83.9%, p=.39), latency prolonged by ≥ 48 hr (75.1% vs 77.4%, p=.59) or histological chorioamnionitis (50.0% vs 47.6%, p=.73). After applying propensity scores and assigning inverse probability of treatment weighting, tocolysis was not associated with improved survival without severe morbidity as compared with no tocolysis (odds ratio 1.01 [95% Confidence Interval 0.94-1.09], latency prolonged by ≥ 48 hr (1.03 [0.95-1.11]), or histological chorioamnionitis (1.03 [0.92-1.17]). There was no association between the initial tocolytic drug used (oxytocin receptor antagonists or calcium-channel blockers vs no

tocolysis) and the three outcomes. Sensitivity analyses of women (1) with preterm premature rupture of membranes at 26 to 31 weeks' gestation, (2) who delivered at least 12 hr after rupture of membranes, with direct admission after the rupture of membranes and (3) presence or (4) absence of contractions, gave similar results.

Conclusion: Tocolysis in cases of preterm premature rupture of membranes is not associated with improved obstetric or neonatal outcomes; its clinical benefit remains un-proven.

Key words: EPIPAGE 2, preterm premature rupture of membranes, tocolysis, propensity score, survival, prematurity, severe morbidity, chorioamnionitis, latency.

Introduction

Preterm premature rupture of membranes (PPROM) is responsible for one third of preterm births[1] and represents a major cause of neonatal mortality and morbidity.[1–3] Recommended clinical care before 34 weeks' gestation, in the absence of labor, chorioamnionitis or fetal distress, include antenatal steroids, antibiotics and expectant management to reduce prematurity and its adverse neonatal consequences.[4–7]

However, the use of tocolysis in cases of PPROM remains controversial.[4,8] Indeed, delaying delivery may allow for prenatal corticosteroids and *in utero* transfer and reduce neonatal morbidity due to prematurity. But it may also prolong fetal exposure to maternofetal infection thereby increasing the risks of neonatal morbidity and mortality.

Only a few randomized controlled trials have addressed this issue, with different primary outcomes and conflicting results.[9–18] These trials have small sample sizes, and most are old with obstetric interventions inconsistent with current practices, thus limiting the external validity and reliability of their findings. In some cases, the study design limited the inclusion of women with active contractions and therefore the applicability of the results to "real-life" practice.[10,14,15,18] Even without strong evidence of its usefulness,[5] tocolysis is widely prescribed to delay delivery and provide adequate prenatal care.[19,20] In France, in the absence of clear recommendations,[4] the use of tocolysis after PPROM varies according to the health center and its local policy.[20]

To investigate whether tocolysis administration was associated with improved neonatal and obstetric outcomes after PPROM, we performed a secondary analysis of a national population-based prospective cohort of preterm infants recruited in France in 2011.[21]

Materials and Methods

This a secondary analysis of EPIPAGE 2 (Etude épidémiologique sur les petits âges gestationnels 2), a prospective, national, population-based cohort study that was implemented

153 to describe short- and long-term outcomes among preterm infants from birth to 12 years old
154 as a function of their birth circumstances, including medical interventions and organization of
155 care.[21]

156 *Setting and data collection of the EPIPAGE 2 cohort study*

157 Briefly, eligible participants included all live births, stillbirths and terminations of pregnancy
158 at $22^{0/7}$ to $34^{6/7}$ weeks' gestation from March to December 2011 in 25 French regions
159 involving 546 maternity units, whose parents had not declined to participate. Infants were
160 recruited during 3 different periods by gestational age at birth: 8-month recruitment for births
161 at 22-26 completed weeks' gestation, 6-month recruitment for births at 27-31 weeks, and 5-
162 week recruitment for births at 32-34 weeks. Extremely preterm births (22-26 weeks) were
163 recruited during a longer period because of their very low incidence and only a sample of
164 moderate preterm births (32-34 weeks) was recruited.[21] Maternal, obstetric, and neonatal data
165 were collected following a standardized protocol. Full details of the cohort recruitment and
166 data collection were previously reported elsewhere.[21]

167 *Ethics*

168 As required by French law and regulations, EPIPAGE 2 was approved by the national data
169 protection authority (Comission Nationale de l'Informatique et des Libertés, CNIL
170 n°911009), the appropriate ethics committees (CCTIRS: Comité Consultatif sur le Traitement
171 de l'Information en matière de Recherche, approval granted November 18, 2010) and the
172 committee for the protection of people participating in biomedical research (CPP: Comité de
173 Protection des Personnes, approval granted March 18, 2011).

174 *Participants*

175 In the present study we included women with PPROM at 24 to 32 completed weeks'
176 gestation, with a single fetus alive at the time of PPROM and born between 24 and 34 weeks.
177 PPROM was defined as spontaneous rupture of membranes occurring before admission to a

delivery room and diagnosed at least two hours before birth. As recommended, the diagnosis was based on maternal history and sterile speculum examination with a diagnostic test if necessary.[4,5] Women with multiple pregnancies (n=2020), terminations of pregnancy (n=1292), homebirths (n=54), fetal death before maternal admission at hospital (n=675), lethal malformations (n=103) and precursor to delivery other than PPROM (n=2220) were excluded. We also excluded infants with care limitations due to an antenatal diagnosis of poor prognosis (n=8). Care limitations were defined as antenatal decisions not to perform a cesarean section, not to resuscitate the newborn, or to proceed to palliative care after birth. All mothers with a contraindication to tocolysis (i.e. abruptio placentae, vaginal bleeding, hyperthermia, cord prolapsed or maternal pathology) were excluded (n=24), as were women with < 2 hr from PPROM diagnosis to delivery (n=47).

French guidelines

Guidelines from the National College of French Gynecologists and Obstetricians state that tocolysis can be administered after PPROM with uterine contractions up to 33 completed weeks' gestation.[4] Recommended tocolytic agents are calcium-channel blockers (nifedipine, nicardipine), oxytocin-receptor blockers (atosiban) and, although rarely used, beta mimetics (salbutamol). Magnesium sulfate was not routinely used for tocolysis or neuroprotection in 2011.

Main outcomes and exposition measures

The primary outcome was survival to discharge without severe neonatal morbidity.[22] Survival was defined as the number of children discharged alive from hospital relative to the number of fetuses alive at the time of PPROM. Severe neonatal morbidity was defined as any of the following: severe intraventricular haemorrhage (IVH) defined as IVH associated with ventricular dilatation (grade III IVH) and intraparenchymal hemorrhage (i.e., large unilateral parenchymal hyperdensity or large unilateral porencephalic cyst)[23]; cystic periventricular

leukomalacia (i.e., periventricular white matter echolucencies at ultrasonography)[24]; stages II or III necrotizing enterocolitis according to Bell's staging[25]; stage 3 or greater retinopathy of prematurity according to international classification[26] and/or laser treatment; and severe bronchopulmonary dysplasia defined as requiring oxygen for at least 28 days in addition to the requirement of 30% or more oxygen and/or mechanical ventilator support or continuous positive airway pressure at 36 weeks' postmenstrual age.[27]

The secondary outcome was prolongation of gestation, defined as latency period (i.e., time from rupture to delivery) ≥ 48 hr. Prolongation of gestation after PPROM can induce prolonged fetal exposure to infection, with adverse consequences. We thus studied a third outcome: histological chorioamnionitis with or without funisitis (infection/inflammation of the fetal membranes with potential extension to the umbilical cord), diagnosed by the gold standard, i.e. histological examination of the placenta.[28] The main exposure was the administration of any tocolytic treatment after PPROM diagnosis (coded as tocolysis vs no tocolysis).

Definition of other studied factors

Gestational age (GA) was determined as the best obstetrical estimate combining last menstrual period and first trimester ultrasonography assessment. Uterine contractions were assessed from uterine activity tracings recorded at admission. Administration of antenatal steroids was a binary variable categorized as "at least one injection" versus "no injection" so as to not introduce a temporality notion (i.e., complete course defined by two injections of betamethasone at a 24-hr interval) related to tocolysis effectiveness. Clinical chorioamnionitis was defined as maternal temperature ≥ 37.8°C (100°F) during delivery with any two of the following criteria: uterine tenderness, purulent or foul-smelling amniotic fluid, maternal tachycardia, fetal tachycardia, maternal leukocytosis ≥ 15,000 cells/mm^3. Z-score birth weights were calculated from Gardosi's intrauterine growth curves corrected for sex and

gestational age.[29] Early-onset sepsis was diagnosed by positive bacteriology findings in blood or cerebrospinal fluid (confirmed infection) beginning during the first 3 days of life.

Statistical analysis

Categorical variables were compared by chi-square or Fisher's exact test as appropriate. Means and medians of quantitative variables were compared by Student's *t* test and Mann–Whitney U test, respectively. All percentages and medians were weighted according to the duration of the recruitment periods by gestational age. Statistical significance was set at two-tailed $p < .05$.

We used a propensity-score analysis to minimize the indication bias in estimating the treatment effect.[30] The propensity score was defined as the woman's probability of receiving tocolysis conditional on uterine contractions at admission and individual covariates. The first step in the analysis consisted of estimating the normalized score by using a logistic regression model with tocolysis as the dependent variable, regressed by baseline characteristics selected from the literature and clinical considerations, excluding covariates that might be affected by the treatment.[31] We considered characteristic of the health center (type of maternity ward), maternal characteristics (age, country of birth), individual clinical factors (uterine contractions at admission, gestational age at PPROM, PPROM before hospitalization, fetal gender, presentation, and birth weight < 3rd percentile of the normalized z-score as a proxy for intra-uterine growth restriction), and antenatal management (*in utero* transfer and administration of antenatal steroids or antibiotics), depending on the outcome. The propensity scores therefore take into account the possible indications for tocolysis administration (therapeutic or prophylactic). Gestational age at birth was not considered in the models because it can be a result of tocolysis administration. The second step in the analysis involved inverse probability of treatment weighting (IPTW), based on estimated propensity scores, to obtain a synthetic population in which treatment assignment is independent of measured baseline covariates, as

confirmed by balance diagnostics.[30,32] We finally estimated the association between tocolysis and outcomes by a logistic regression model within the weighted sample, obtaining odds ratios (ORs) and 95% confidence intervals (95% CIs) with robust standard errors.

Six sensitivity analyses were performed. We first investigated the association between the initial tocolysis drug used (oxytocin receptor antagonists, n=267, or calcium-channel blockers, n=287, vs no tocolysis) and the three outcomes, with similar methodologies. Antenatal management, including tocolysis administration, might differ by GA at PPROM and induce a residual indication bias, so we analyzed women with PPROM at 26 to 31 completed weeks' gestation (n=549). The fourth sensitivity analysis focused on women who delivered at least twelve hours after PPROM (n=686), to control for the low threshold initially chosen to define PPROM not resulting in including women with membranes ruptured during labor. Finally, we restricted the population to women with direct admission after PPROM (i.e. without *in utero* transfer) and with (n=115) or without (n=135) uterine contractions to investigate tocolysis consequences for specific subgroups.

The proportion of missing data ranged from 0% to 7.5% for each covariate, and missing data were considered missing at random. Multiple imputation involved use of all baseline variables and outcomes of the propensity-score model. A propensity score was estimated for each of the 30 imputed datasets generated, and results were pooled for a final analysis according to Rubin's rules.

At the conventional two-tailed significance level of 0.05, and based on the fixed sample size, our study had 80% statistical power to show an OR of 1.1 quantifying the association between tocolysis and improved survival without major morbidity. Data were analyzed by use of Stata/SE 13.0 (StataCorp LP, College Station, TX, USA).

Results

Among the 803 women with PPROM at 24 to 32 weeks' gestation, with singletons alive at PPROM and without contraindication to tocolysis, 596 (weighted percentage 73.4%) received tocolysis after PPROM and 207 (weighted percentage 26.6%) did not (Figure 1). The proportion of participants who received tocolysis was similar for each subgroup of gestational age at PPROM: 76.6% at 24 to 26 weeks' gestation, 74.1% at 27 to 29 weeks and 71.8% at 30 to 32 weeks (p=.55).

Maternal, obstetric and center characteristics with and without tocolysis administration are presented in Table 1. Treatment groups did not differ in median gestational age at PPROM and at birth. Median latency durations were similar: 6 versus 5 days without and with tocolysis (p=.26). Women who were transferred from another hospital more frequently received tocolysis, as had women with uterine contractions at admission. Antibiotics and antenatal steroids use were respectively > 95% and > 89%, whatever the treatment group.

In total, 619 children survived until discharge without severe morbidity (weighted percentage 85.9% [95% CI 83.1-88.3]); for 597 (weighted percentage 75.7% [71.4-79.5]), the latency period was prolonged by $\geq$ 48 hr (Table 2). When placental examination was performed (n=494), histological chorioamnionitis was diagnosed in 280 cases (weighted percentage 49.5% [43.5-55.5]). There was no association between the tocolysis group and these three outcomes, nor when stratifying by gestational age at PPROM. The risk of *in utero* fetal demise after PPROM was similar in both groups (1.0% vs 1.0%, p=.96). The incidence of early-onset sepsis, severe cerebral lesion, severe bronchopulmonary dysplasia, necrotizing enterocolitis and retinopathy did not differ by treatment group (Table A.1).

Propensity scores were calculated for each woman and for each outcome. Mean propensity score and covariates were balanced across treatment and comparison groups within the 5 blocks of propensity scores. Moreover, standardized differences in the weighted samples were

less than 10%. These diagnostic assessments suggest that for each outcome, IPTW created a sample in which the distributions of baseline-measured covariates were similar with and without tocolysis. Tocolysis after PPROM was not associated with survival at discharge without severe morbidity or latency prolonged by ≥ 48 hr (OR=1.01 [95% CI 0.94-1.09] and 1.03 [0.95-1.11], respectively) (Table 3).

To assess whether tocolysis could increase intra-uterine inflammation, we investigated the association of tocolysis and histological chorioamnionitis in the subgroup of 494 women with placental examination and found no increase in histological chorioamnionitis with tocolysis (OR=1.03 [0.92-1.17]).

The initial tocolytic agents were mainly oxytocin receptor antagonists (267 women) and calcium-channel blockers (287 women). As compared with no tocolysis, the type of initial drug was not associated with the three outcomes (Table A.2).

We performed a sensitivity analysis including 549 women with PPROM at 26 to 31 weeks' gestation, of whom 413 (weighted percentage 75.4%) received tocolysis, and found no association between tocolysis and survival at discharge without severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis (OR=1.06 [0.98-1.15], 1.04 [0.95-1.14], and 1.03 [0.88-1.19], respectively) (Table 3). We also investigated a subgroup of 686 women who delivered at least 12 hr after rupture of membranes, of whom 514 (weighted percentage 73.5%) received tocolysis, and found no association between tocolysis and the three outcomes (OR=1.01 [0.93-1.10], 1.05 [0.97-1.13] and 1.05 [0.92-1.20], respectively) (Table 3). Among women with direct admission after PPROM, respectively 68.5% and 51.3% had therapeutic or prophylactic tocolysis. In these specific subgroups, there was no association between tocolysis and the three outcomes (Table A.3).

Comment

Main findings

Our study shows that in cases of preterm births related to PPROM, tocolysis administration is not associated with survival at discharge without severe morbidity or with delivery delayed by ≥ 48 hr after PPROM. Additionally, the rate of histological chorioamnionitis is similar with and without tocolysis after PPROM.

Strengths and limitations

Strengths of our study include a large sample of women with contemporary obstetric management including a high rate of antenatal steroids and antibiotics. We believe our study findings allow for an assessment of routine clinical management practices in the paucity of data from well-constructed and up-to-date randomized control trials. Indeed, currently available trials specifically addressing tocolysis administration after PPROM were published more than 20 years ago,[9,10,12,14–16,33,34] had small sample size (6 to 81 patients), or featured bias (e.g. performance and detection biases with no blinding of the participants or researchers,[12–16] or reporting bias with outcomes not pre-specified or not explicitly stated[9,16]). Antibiotics and steroids were not consistently administered resulting in a substantial limitation in the reliability and external validity of the results. In contrast to most randomized trials,[10,14,15,18] we included all women for whom tocolysis was potentially useful, including those with regular contractions.

Neonatal prognosis was considered the relevant clinical outcome to set as a primary outcome. Indeed, prolongation of gestation is not an objective but a step in the pathway to improve perinatal morbidity and mortality. Randomized trials designed to show a significant difference in latency duration as a primary outcome can be underpowered to find a significant difference in neonatal mortality or morbidity.[9,11,12,14,15]

This study was, however, limited by the design of the EPIPAGE 2 cohort: treatment assignment was not random with the observational data. A new randomized controlled trial would help define the best management, but in these anxiety-provoking situations, trials are difficult to achieve. For illustration, in the APOSTEL IV trial, 50 women were randomized in 27 months while the expected number was 120.[18] With these observational data, we compared treatment strategies under the usual conditions, simulating a hypothetical pragmatic randomized trial.[35] To address the indication bias, we used a propensity-score method to obtain unbiased estimates of average treatment effects and followed the most recent best practices for the use of IPTW.[32] This method provided a way to balance measured covariates across treated and control groups. The precise indication for tocolysis was not specified in the EPIPAGE 2 cohort study. Tocolysis can be given to patients with contractions after PPROM (therapeutic tocolysis) or without contractions (prophylactic tocolysis). We thus included in the propensity score the variable indicating contractions at admission and performed sensitivity analyses by stratifying on contractions at admission, with consistent findings.

We considered that within two hours after PPROM diagnosis, the obstetrics team had enough time to give tocolysis if deemed necessary. However, choosing a fairly low threshold between PPROM diagnosis and birth may have induced a selection bias by including women with membranes ruptured during labor. We therefore tested the robustness of our analysis by using a 12-hr threshold, which gave similar results.

Another limitation involves the truncated population for cases of PPROM delivered after 35 weeks. Late-preterm births were indeed not considered in the EPIPAGE 2 design. Therefore, we studied only women with PPROM at 24 to 32 weeks and likely missed only a very few births with the longest latency durations and the best prognosis.[36]

Placental histology was not systematically performed. Absence of examination was associated with late gestational age, absence of clinical chorioamnionitis and delivery in a type 2

maternity ward. Data were not missing at random, so we did not perform multiple imputation. It is possible that we missed examinations for the healthiest infants and as a result slightly overestimated the association between tocolysis administration and chorioamnionitis.

Interpretation

Our main neonatal finding is in line with recent publications,[8,18] including a meta-analysis (8 randomized controlled trials, 408 women with PPROM) which showed that tocolysis was not associated with neonatal outcome improvement as compared with no tocolysis.[8] However, our results bring further explanations for this negative result, relying on the lack of difference in the prolongation of pregnancy and on the incidence of histological chorioamnionitis unrelated to tocolysis use. These two last findings contrast with the conclusions of the meta-analysis, and may be possibly explained by the beneficial impact of antibiotic administration[7] widely used in our sample for women with and without tocolysis or the use of a different definition for chorioamnionitis (clinical vs histological).

Finally, it should be noted that the magnitude of the between-group difference was small and with limited clinical relevance. Tocolysis might thus be considered an ineffective intervention in the setting of PPROM.[18]

Although most women presenting PPROM and delivering prematurely received tocolysis, the treatment was not associated with neonatal outcome or prolonged gestation by $\geq$ 48 hr. These results do not support tocolytic therapy for women with PPROM and emphasize the need for a large randomized controlled trial designed to study the impact of tocolysis on neonatal outcomes.

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List of tables:

606 **Table 1: Maternal, obstetric and center characteristics without and with tocolysis**
607 **administration after preterm premature rupture of membranes (PPROM)**

Characteristics	No tocolysis (n=207)	Tocolysis (n=596)	P value
Maternal characteristics			
Age (years), 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 (days), 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 before labor	80 (38.7)	206 (30.5)	
Mode of delivery (n=798)			.11
Vaginal delivery	94 (44.2)	300 (55.9)	
Cesarean before labor	80 (38.8)	206 (30.6)	
Cesarean 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
Birth weight ≤ 3rd 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)	

608
609 Data are n (%) unless indicated. Percentages are weighted by recruitment period.
610 IQR, interquartile range; WG, weeks' gestation.
611 The two groups were compared by Mann Whitney test for medians and chi-square or Fisher's exact test for
612 categorical variables.
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Table 2: Survival without severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis without and with tocolysis administration after PPROM

Outcome GA at PPROM (wk)	Total	No tocolysis	Tocolysis	p.value
	n/N (%)	n/N (%)	n/N (%)	
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 hr	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

[a] Percentages are weighted by recruitment period.

[b] Among the histological examinations carried out.

The two groups were compared by chi-square or Fisher's exact test.

GA, gestational age

Table 3: Association between tocolysis administration after PPROM and survival without severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis after inverse probability of treatment weighting

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

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 gender, presentation, birth weight < 3rd percentile of the normalized z-score.

[b] 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 gender, presentation, birth weight < 3rd percentile of the normalized z-score.

[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, presentation.

[d] Obtained after multiple imputation.

[e] For performed placental examination.

Table A.1: Detailed neonatal outcomes without and with tocolysis administration

Outcome GA at PPROM (wk)	Total	No tocolysis	Tocolysis	p.value
	n/N (%[a])	n/N (%[a])	n/N (%[a])	
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

[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 haemorrhage, intraparenchymal hemorrhage or cystic periventricular leukomalacia

Table A.2: Association between the initial tocolytic drug after PPROM and survival without severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis after inverse probability of treatment weighting

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

[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 gender, presentation, birth weight < 3rd percentile of the normalized z-score.

[b] 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 gender, presentation, birth weight < 3rd percentile of the normalized z-score.

[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, presentation.

[d] Obtained after multiple imputation.

[e] For performed placental examination.

Table A.3: Association between tocolysis administration after PPROM and survival without severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis in women admitted directly after PPROM, with and without contractions

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

[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 gender, presentation, birth weight < 3rd percentile of the normalized z-score.

[b] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, antenatal steroids, antibiotics, fetal gender, presentation, birth weight < 3rd percentile of the normalized z-score.

[c] Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at PPROM, antenatal steroids, antibiotics, presentation.

[d] Obtained after multiple imputation.

[e] For performed placental examination.

Figure legends:

Title:

Figure 1: Flow chart of the patients in the study

Description of figure 1:

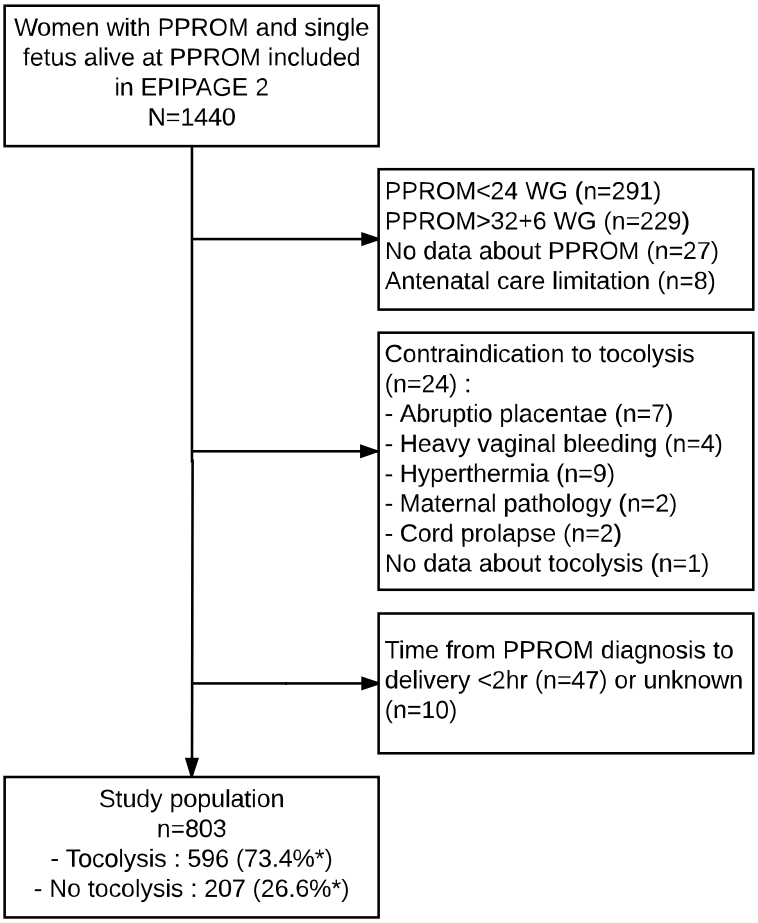
The flow chart summarizes how the sample size of the analysis was reached.

Legends of figure 1:

WG: weeks' gestation

PPROM: preterm premature rupture of membranes

* Percentages are weighted by recruitment period.


Women with PPROM and single fetus alive at PPROM included in EPIPAGE 2
N=1440
PPROM<24 WG (n=291)
PPROM>32+6 WG (n=229)
No data about PPROM (n=27)
Antenatal care limitation (n=8)
Contraindication to tocolysis (n=24) :
- Abruptio placentae (n=7)
- Heavy vaginal bleeding (n=4)
- Hyperthermia (n=9)
- Maternal pathology (n=2)
- Cord prolapse (n=2)
No data about tocolysis (n=1)
Time from PPROM diagnosis to delivery <2hr (n=47) or unknown (n=10)
Study population
n=803
- Tocolysis : 596 (73.4%*)
- No tocolysis : 207 (26.6%*)