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1 **Tocolysis after preterm premature rupture of membranes and neonatal outcome: a**
2 **propensity-score analysis**

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43
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48 **Condensation:** Although frequently administered, tocolysis after preterm premature rupture
49 of membranes is not associated with improved neonatal outcome, prolonged gestation or
50 increased rate of histological chorioamnionitis.

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52 **Short title:** Tocolysis after PPROM and neonatal outcome

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78 **Abstract**

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

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

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

94 **Results:** The study population consisted of 803 women; 596 (73.4%) received tocolysis.
95 Women with and without tocolysis did not differ in neonatal survival without severe
96 morbidity (86.7% vs 83.9%, $p=.39$), latency prolonged by ≥ 48 hr (75.1% vs 77.4%, $p=.59$) or
97 histological chorioamnionitis (50.0% vs 47.6%, $p=.73$). After applying propensity scores and
98 assigning inverse probability of treatment weighting, tocolysis was not associated with
99 improved survival without severe morbidity as compared with no tocolysis (odds ratio 1.01
100 [95% Confidence Interval 0.94-1.09], latency prolonged by ≥ 48 hr (1.03 [0.95-1.11]), or
101 histological chorioamnionitis (1.03 [0.92-1.17])). There was no association between the initial
102 tocolytic drug used (oxytocin receptor antagonists or calcium-channel blockers vs no

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

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

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

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128 **Introduction**

129 Preterm premature rupture of membranes (PPROM) is responsible for one third of preterm
130 births¹ and represents a major cause of neonatal mortality and morbidity.¹⁻³ Recommended
131 clinical care before 34 weeks' gestation, in the absence of labor, chorioamnionitis or fetal
132 distress, include antenatal steroids, antibiotics and expectant management to reduce
133 prematurity and its adverse neonatal consequences.⁴⁻⁷

134 However, the use of tocolysis in cases of PPRM remains controversial.^{4,8} Indeed, delaying
135 delivery may allow for prenatal corticosteroids and *in utero* transfer and reduce neonatal
136 morbidity due to prematurity. But it may also prolong fetal exposure to maternofetal infection
137 thereby increasing the risks of neonatal morbidity and mortality.

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

147 To investigate whether tocolysis administration was associated with improved neonatal and
148 obstetric outcomes after PPRM, we performed a secondary analysis of a national
149 population-based prospective cohort of preterm infants recruited in France in 2011.²¹

150 **Materials and Methods**

151 This a secondary analysis of EPIPAGE 2 (Etude épidémiologique sur les petits âges
152 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

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

189 *French guidelines*

190 Guidelines from the National College of French Gynecologists and Obstetricians state that
191 tocolysis can be administered after PPRM with uterine contractions up to 33 completed
192 weeks' gestation.⁴ Recommended tocolytic agents are calcium-channel blockers (nifedipine,
193 nicardipine), oxytocin-receptor blockers (atosiban) and, although rarely used, beta mimetics
194 (salbutamol). Magnesium sulfate was not routinely used for tocolysis or neuroprotection in
195 2011.

196 *Main outcomes and exposition measures*

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

203 leukomalacia (i.e., periventricular white matter echolucencies at ultrasonography)²⁴; stages II
204 or III necrotizing enterocolitis according to Bell's staging²⁵; stage 3 or greater retinopathy of
205 prematurity according to international classification²⁶ and/or laser treatment; and severe
206 bronchopulmonary dysplasia defined as requiring oxygen for at least 28 days in addition to
207 the requirement of 30% or more oxygen and/or mechanical ventilator support or continuous
208 positive airway pressure at 36 weeks' postmenstrual age.²⁷

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

217 *Definition of other studied factors*

218 Gestational age (GA) was determined as the best obstetrical estimate combining last
219 menstrual period and first trimester ultrasonography assessment. Uterine contractions were
220 assessed from uterine activity tracings recorded at admission. Administration of antenatal
221 steroids was a binary variable categorized as "at least one injection" versus "no injection" so
222 as to not introduce a temporality notion (i.e., complete course defined by two injections of
223 betamethasone at a 24-hr interval) related to tocolysis effectiveness. Clinical chorioamnionitis
224 was defined as maternal temperature \geq 37.8°C (100°F) during delivery with any two of the
225 following criteria: uterine tenderness, purulent or foul-smelling amniotic fluid, maternal
226 tachycardia, fetal tachycardia, maternal leukocytosis \geq 15,000 cells/mm³. Z-score birth
227 weights were calculated from Gardosi's intrauterine growth curves corrected for sex and

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

230 *Statistical analysis*

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

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

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

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

267 The proportion of missing data ranged from 0% to 7.5% for each covariate, and missing data
268 were considered missing at random. Multiple imputation involved use of all baseline variables
269 and outcomes of the propensity-score model. A propensity score was estimated for each of the
270 30 imputed datasets generated, and results were pooled for a final analysis according to
271 Rubin's rules.

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

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277

278 **Results**

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

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

291 In total, 619 children survived until discharge without severe morbidity (weighted percentage
292 85.9% [95% CI 83.1-88.3]); for 597 (weighted percentage 75.7% [71.4-79.5]), the latency
293 period was prolonged by ≥ 48 hr (Table 2). When placental examination was performed
294 ($n=494$), histological chorioamnionitis was diagnosed in 280 cases (weighted percentage
295 49.5% [43.5-55.5]). There was no association between the tocolysis group and these three
296 outcomes, nor when stratifying by gestational age at PPRM. The risk of *in utero* fetal
297 demise after PPRM was similar in both groups (1.0% vs 1.0%, $p=.96$). The incidence of
298 early-onset sepsis, severe cerebral lesion, severe bronchopulmonary dysplasia, necrotizing
299 enterocolitis and retinopathy did not differ by treatment group (Table A.1).

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

303 less than 10%. These diagnostic assessments suggest that for each outcome, IPTW created a
304 sample in which the distributions of baseline-measured covariates were similar with and
305 without tocolysis. Tocolysis after PPRM was not associated with survival at discharge
306 without severe morbidity or latency prolonged by ≥ 48 hr (OR=1.01 [95% CI 0.94-1.09] and
307 1.03 [0.95-1.11], respectively) (Table 3).

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

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

315 We performed a sensitivity analysis including 549 women with PPRM at 26 to 31 weeks'
316 gestation, of whom 413 (weighted percentage 75.4%) received tocolysis, and found no
317 association between tocolysis and survival at discharge without severe morbidity, latency
318 prolonged by ≥ 48 hr and histological chorioamnionitis (OR=1.06 [0.98-1.15], 1.04 [0.95-
319 1.14], and 1.03 [0.88-1.19], respectively) (Table 3). We also investigated a subgroup of 686
320 women who delivered at least 12 hr after rupture of membranes, of whom 514 (weighted
321 percentage 73.5%) received tocolysis, and found no association between tocolysis and the
322 three outcomes (OR=1.01 [0.93-1.10], 1.05 [0.97-1.13] and 1.05 [0.92-1.20], respectively)
323 (Table 3). Among women with direct admission after PPRM, respectively 68.5% and 51.3%
324 had therapeutic or prophylactic tocolysis. In these specific subgroups, there was no
325 association between tocolysis and the three outcomes (Table A.3).

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327

328 **Comment**

329 *Main findings*

330 Our study shows that in cases of preterm births related to PPRM, tocolysis administration is
331 not associated with survival at discharge without severe morbidity or with delivery delayed by
332 ≥ 48 hr after PPRM. Additionally, the rate of histological chorioamnionitis is similar with
333 and without tocolysis after PPRM.

334 *Strengths and limitations*

335 Strengths of our study include a large sample of women with contemporary obstetric
336 management including a high rate of antenatal steroids and antibiotics. We believe our study
337 findings allow for an assessment of routine clinical management practices in the paucity of
338 data from well-constructed and up-to-date randomized control trials. Indeed, currently
339 available trials specifically addressing tocolysis administration after PPRM were published
340 more than 20 years ago,^{9,10,12,14-16,33,34} had small sample size (6 to 81 patients), or featured
341 bias (e.g. performance and detection biases with no blinding of the participants or
342 researchers,¹²⁻¹⁶ or reporting bias with outcomes not pre-specified or not explicitly stated^{9,16}).

343 Antibiotics and steroids were not consistently administered resulting in a substantial
344 limitation in the reliability and external validity of the results. In contrast to most randomized
345 trials,^{10,14,15,18} we included all women for whom tocolysis was potentially useful, including
346 those with regular contractions.

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

352 This study was, however, limited by the design of the EPIPAGE 2 cohort: treatment
353 assignment was not random with the observational data. A new randomized controlled trial
354 would help define the best management, but in these anxiety-provoking situations, trials are
355 difficult to achieve. For illustration, in the APOSTEL IV trial, 50 women were randomized in
356 27 months while the expected number was 120.¹⁸ With these observational data, we compared
357 treatment strategies under the usual conditions, simulating a hypothetical pragmatic
358 randomized trial.³⁵ To address the indication bias, we used a propensity-score method to
359 obtain unbiased estimates of average treatment effects and followed the most recent best
360 practices for the use of IPTW.³² This method provided a way to balance measured covariates
361 across treated and control groups. The precise indication for tocolysis was not specified in the
362 EPIPAGE 2 cohort study. Tocolysis can be given to patients with contractions after PPRM
363 (therapeutic tocolysis) or without contractions (prophylactic tocolysis). We thus included in
364 the propensity score the variable indicating contractions at admission and performed
365 sensitivity analyses by stratifying on contractions at admission, with consistent findings.

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

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

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

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

380 *Interpretation*

381 Our main neonatal finding is in line with recent publications,^{8,18} including a meta-analysis (8
382 randomized controlled trials, 408 women with PPROM) which showed that tocolysis was not
383 associated with neonatal outcome improvement as compared with no tocolysis.⁸ However, our
384 results bring further explanations for this negative result, relying on the lack of difference in
385 the prolongation of pregnancy and on the incidence of histological chorioamnionitis unrelated
386 to tocolysis use. These two last findings contrast with the conclusions of the meta-analysis,
387 and may be possibly explained by the beneficial impact of antibiotic administration⁷ widely
388 used in our sample for women with and without tocolysis or the use of a different definition
389 for chorioamnionitis (clinical vs histological).

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

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

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399

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580 **List of tables:**

581

582 Table 1: Maternal, obstetric and center characteristics without and with tocolysis

583 administration after preterm premature rupture of membranes (PPROM)

584 Table 2: Survival without severe morbidity, latency prolonged by ≥ 48 hr and histological

585 chorioamnionitis without and with tocolysis administration after PPRM

586 Table 3: Association between tocolysis administration after PPRM and survival without

587 severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis after inverse

588 probability of treatment weighting

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

590 Table A.2: Association between the initial tocolytic drug after PPRM and survival without

591 severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis after inverse

592 probability of treatment weighting

593 Table A.3: Association between tocolysis administration after PPRM and survival without

594 severe morbidity, latency prolonged by ≥ 48 hr and histological chorioamnionitis in women

595 admitted directly after PPRM, with and without contractions

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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 PPRM (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
<i>In utero</i> 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 \leq 3 rd 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)	

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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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618 **Table 2: Survival without severe morbidity, latency prolonged by ≥ 48 hr and**
 619 **histological chorioamnionitis without and with tocolysis administration after PPROM**
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Outcome	Total	No tocolysis	Tocolysis	p.value
GA at PPROM (wk)	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

621 ^a Percentages are weighted by recruitment period.

622 ^b Among the histological examinations carried out.

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

624 GA, gestational age

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

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644 WG: weeks' gestation

645 ^a Covariates used to estimate the propensity score: type of maternity unit, country of mother's birth, maternal
 646 age, gestational age at PPROM, PPROM before hospitalization, presence of contractions at admission, *in utero*
 647 transfer, antenatal steroids, antibiotics, fetal gender, presentation, birth weight < 3rd percentile of the normalized
 648 z-score.

649 ^b Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at
 650 PPROM, PPROM before hospitalization, presence of contractions at admission, *in utero* transfer, antenatal
 651 steroids, antibiotics, fetal gender, presentation, birth weight < 3rd percentile of the normalized z-score.

652 ^c Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at
 653 PPROM, PPROM before hospitalization, presence of contractions at admission, *in utero* transfer, antenatal
 654 steroids, antibiotics, presentation.

655 ^d Obtained after multiple imputation.

656 ^e For performed placental examination.

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666 **Table A.1: Detailed neonatal outcomes without and with tocolysis administration**
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Outcome GA at PPRM (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

668 GA, gestational age

669 ^a Percentages are weighted by recruitment period.

670 ^b Among infants transferred to a neonatal intensive care unit

671 ^c Among infants alive at discharge

672 ^d Severe cerebral lesion include grade III intraventricular haemorrhage, intraparenchymal hemorrhage or cystic
 673 periventricular leukomalacia

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

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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)

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690 ^a Covariates used to estimate the propensity score: type of maternity unit, country of mother's birth, maternal
 691 age, gestational age at PPRM, PPRM before hospitalization, presence of contractions at admission, *in utero*
 692 transfer, antenatal steroids, antibiotics, fetal gender, presentation, birth weight < 3rd percentile of the normalized
 693 z-score.

694 ^b Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at
 695 PPRM, PPRM before hospitalization, presence of contractions at admission, *in utero* transfer, antenatal
 696 steroids, antibiotics, fetal gender, presentation, birth weight < 3rd percentile of the normalized z-score.

697 ^c Covariates used to estimate the propensity score: type of maternity unit, maternal age, gestational age at
 698 PPRM, PPRM before hospitalization, presence of contractions at admission, *in utero* transfer, antenatal
 699 steroids, antibiotics, presentation.

700 ^d Obtained after multiple imputation.

701 ^e For performed placental examination.

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710 **Table A.3: Association between tocolysis administration after PPROM and survival**
 711 **without severe morbidity, latency prolonged by ≥ 48 hr and histological**
 712 **chorioamnionitis in women admitted directly after PPROM, with and without**
 713 **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)

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 717 ^a Covariates used to estimate the propensity score: type of maternity unit, country of mother's birth, maternal
 718 age, gestational age at PPROM, antenatal steroids, antibiotics, fetal gender, presentation, birth weight < 3rd
 719 percentile of the normalized z-score.

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

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

725 ^d Obtained after multiple imputation.

726 ^e For performed placental examination.

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735 **Figure legends:**

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737 Title:

738 Figure 1: Flow chart of the patients in the study

739 Description of figure 1:

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

741 Legends of figure 1:

742 WG: weeks' gestation

743 PPROM: preterm premature rupture of membranes

744 * Percentages are weighted by recruitment period.

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