OBSTETRICS

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

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

OBJECTIVE: The objective of the study was to investigate whether tocolytic therapy in cases of preterm premature rupture of membranes is associated with improved neonatal or obstetric outcomes.

STUDY DESIGN: Etude Epidémiologique sur les Petits Ages Gestationnels 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 24−32 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 hours (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 hours (1.03 [95% confidence interval, 0.95−1.11]), or histological chorioamnionitis (1.03 [95% confidence interval, 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 3 outcomes. Sensitivity analyses of women with preterm premature rupture of membranes at 26−31 weeks' gestation, women who delivered at least 12 hours after rupture of membranes, women with direct admission after the rupture of membranes and the presence or 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 unproven.

Key words: chorioamnionitis, Etude Epidémiologique sur les Petits Ages Gestationnels 2, latency, prematurity, preterm premature rupture of membranes, propensity score, severe morbidity, survival, tocolysis

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, includes 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 related to prematurity. But it may also prolong fetal exposure to maternofetal infection and 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 had 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 Etude Epidémiologique sur les Petits Ages Gestationnels (EPIPAGE) 2, a prospective, national, population-based cohort study that was implemented to describe short- and long-term outcomes among preterm infants from birth to 12 years old as a function of their birth circumstances,

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including medical interventions and organization of care.[21]

Setting and data collection of the EPIPAGE 2 cohort study

Briefly, eligible participants included all live births, stillbirths, and terminations of pregnancy at $22^{0/7}$ to $34^{6/7}$ weeks' gestation from March to December 2011 in 25 French regions involving 546 maternity units, whose parents had not declined to participate. Infants were recruited during 3 different periods by gestational age at birth: 8 month recruitment for births at 22−26 completed weeks' gestation, 6 month recruitment for births at 27−31 weeks, and 5 week recruitment for births at 32−34 weeks.

Extremely preterm births (22−26 weeks) were recruited during a longer period because of their very low incidence, and only a sample of moderate preterm births (32−34 weeks) was recruited.[21] Maternal, obstetric, and neonatal data were collected following a standardized protocol. Full details of the cohort recruitment and data collection were previously reported elsewhere.[21]

Ethics

As required by French law and regulations, EPIPAGE 2 was approved by the national data protection authority (Comission Nationale de l'Informatique et des Libertés, number 911009), the appropriate ethics committees (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche, approval granted Nov. 18, 2010), and the committee for the protection of people participating in biomedical research (Comité de Protection des Personnes, approval granted March 18, 2011).

Participants

In the present study, we included women with PPROM at 24−32 completed weeks' gestation, with a single fetus alive at the time of PPROM and born between 24 and 34 weeks. PPROM was defined as spontaneous rupture of membranes occurring before admission to a delivery room and diagnosed at least 2 hours before birth. As recommended, the diagnosis was based on maternal history and the 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 because of an antenatal diagnosis of poor prognosis (n = 8).

Care limitations were defined as antenatal decisions not to perform a cesarean delivery, not to resuscitate the newborn, or to proceed to palliative care after birth. All mothers with a contraindication to tocolysis (ie, abruptio placentae, vaginal bleeding, hyperthermia, cord prolapse, or maternal pathology) were excluded (n = 24) as were women with <2 hours 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 the 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 hemorrhage (IVH) defined as IVH associated with ventricular dilatation (grade III IVH) and intraparenchymal hemorrhage (ie, large unilateral parenchymal hyperdensity or large unilateral porencephalic cyst)[23]; cystic periventricular leukomalacia (ie, periventricular white matter echolucencies at ultrasonography)[24]; stage 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 (ie, time from rupture to delivery) ≥48 hours. 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 (ie, 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 the last menstrual period and the 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 vs no injection so as to not introduce a temporality notion (ie, complete course defined by 2 injections of betamethasone at a 24 hour interval) related to tocolysis effectiveness.

Clinical chorioamnionitis was defined as a maternal temperature ≥37.8°C (100°F) during delivery with any 2 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 birthweights were calculated from Gardosi's intrauterine growth curves corrected for sex and gestational