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Intentional early delivery versus expectant management for preterm premature rupture of membranes at 28–32 weeks' gestation: A multicentre randomized controlled trial (MICADO STUDY)☆

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ABSTRACT

Objectives: Preterm premature rupture of fetal membranes (PPROM) exposes the fetus to preterm birth, and optimal timing for delivery is controversial. The aim of this study was to compare intentional early delivery ("active management") with expectant management in very preterm birth (28–32 weeks).
Study design: We conducted a prospective randomized controlled trial with intent-to-treat analysis, at 19 tertiary-care hospitals in France and 1 in Geneva, Switzerland. Inclusion criteria were women age ≥18 years, PPROM at $28^{0/7}$ to $31^{6/7}$ weeks' gestation, singleton pregnancy. Exclusion criteria were maternal/fetal indications for immediate delivery. All participants received prophylactic antibiotics (amoxicillin + gentamicin) and two doses of corticosteroids. Women in expectant management delivered at 34 weeks, sooner if medically indicated. Women in active management delivered 24 h after the second steroid dose. The primary outcome measure was a composite of neonatal death/severe adverse events: periventricular leukomalacia, intraventricular hemorrhage, sepsis, oxygen requirement at 36 weeks, and necrotizing enterocolitis. The secondary outcome was clinical chorioamnionitis.
Results: The trial was stopped prematurely, due to recruitment difficulties. Of 360 women assessed, 139 (40% of calculated sample size) were randomized: 70 to expectant management, 69 to active management. Mean gestational age at PPROM was similar in both groups (30 ± 1.3 vs. 30.2 ± 1.2 weeks, respectively). There were 35 cases of medical/suspected complications requiring delivery in expectant management vs. 4 in active management. Mean latency between PPROM and delivery was 11.7 ± 9.8 vs. 2.8 ± 0.6 days, respectively; $P < 0.0001$ (median 8.4 (1.8–44.2) vs. 2.7 (1.9–4.3)). There were more caesarean deliveries in active than expectant management (80% vs. 60%, respectively; $P < 0.01$). There were 2 chorioamnionitis cases, both in expectant management. One baby died in expectant management; 2 in active management (one with heart defect). There was no significant difference in sepsis rates. The combined neonatal death/severe adverse events measure was 12.9% for expectant management and 13.0% for active management (OR 0.98; 95% CI: 0.33–2.93, $P = 0.97$).
Conclusion: For PPROM at 28–32 weeks, and with antenatal antibiotic and steroid therapy, there were no observed differences in neonatal health when comparing expectant management to early delivery. As expected, expectant management resulted in higher gestational age and birth weight. However, our study was underpowered to draw firm and reliable conclusions.

☆ The study was conducted in the Rhône-Alpes region and coordinated in Lyon, France.

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Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide [1]. The premature rupture of fetal membranes (PROM) complicates and precedes approximately one-third of preterm births, exposing the fetus to early onset of labour and potential chorioamnionitis [2–4]. When infection/inflammation are superimposed on prematurity, the consequences for the neonate can be devastating [5–8].

PPROM management has two main goals: reducing fetal immaturity at birth and avoiding chorioamnionitis. Corticosteroid therapy has decreased morbidity in infants born 2–7 days after PPROM [9]. Antenatal antibiotics can prolong the latency period between PPROM and birth by reducing the risk of neonatal infection [10]. However, optimal timing for delivery remains a challenge and is controversial [11]. For PPROM <32–34 weeks' gestation, expectant management is the standard of practice, associated with a higher gestational age at birth and fewer prematurity-linked complications [11–13]. Extension of the latency period nonetheless exposes the fetus to complications such as chorioamnionitis, retroplacental hematoma and fetal distress. Several authors have proposed intentional delivery, hereafter called "active management", as soon as possible after PPROM [14–18]. This strategy could backfire with increased perinatal complications of very preterm birth, such as respiratory distress syndrome or intraventricular hemorrhage. A 2010 Cochrane meta-analysis of 7 randomized controlled trials including 690 women, found insufficient evidence to guide clinical practice, as most trials had methodological weaknesses including small sample size, incompletely defined neonatal outcome measures, and management predating antibiotic and steroid therapies [19]. A 2017 update with 5 additional trials suggested expectant management with observation as potentially safer for mother and baby, with fewer caesarean deliveries and neonatal complications, but added that subgroup analysis at various gestational ages was needed to improve recommendations [20]. The real question therefore becomes, at which gestational age to switch from expectant management to active management. Advances in neonatology and improved neonatal care have overcome the challenges of previous limitations and may promote active management at earlier gestational ages.

In our prospective DOMINOS cohort study of 472 women with PPROM at 24–34 weeks' gestation, we found that: 1) active management after PPROM decreased the risk of adverse neonatal outcomes, as compared to spontaneous labour; and 2) a latency period >14 days was not associated with better neonatal outcomes [21–23]. These observational findings, however, needed to be corroborated with a higher level of evidence, such as a randomized controlled trial (RCT).

The objective of this prospective RCT was to compare active management versus expectant management in PPROM at 28–32 weeks' gestation, namely very preterm birth. This smaller interval was chosen to eliminate the bias of high mortality in extremely preterm birth, while focusing on the gestational ages at high risk for adverse neurodevelopmental outcomes.

Materials and methods

Study design

We conducted a prospective, open-label, randomized clinical trial comparing two strategies of PPROM management (active management vs. expectant management) in 19 hospitals in France and one in Geneva, Switzerland. All hospitals were tertiary care institutions capable of providing comprehensive care for infants <32 weeks' gestational age and/or <1500 g at birth. The study was approved by the *Comité consultatif de protection des personnes dans la recherche biomédicale* (CCPPRB) in France on December 3, 2002 (reference: 2002-113-B) and by the *Commission cantonale d'éthique de la recherche* (CCER) in Geneva, Switzerland. All participants provided written informed consent.

Participants

Women aged ≥18 years were eligible if they presented with PPROM and a singleton pregnancy of $28^{0/7}$ to $31^{6/7}$ weeks' gestation. Clinical diagnosis of membrane rupture was based on a history of amniotic fluid leakage, a sterile speculum examination confirming amniotic fluid drainage from the cervical os, and biochemical tests when in doubt (PROM TEST) [24]. Gestational age was determined from date of last menstrual period or from ultrasound <16 weeks. Where due dates were discordant by >7 days, ultrasound results took precedence. Exclusion criteria were maternal or fetal indications for immediate delivery.

Procedures before randomization

All eligible participants received a standardized protocol for the first 48 h. Vital signs were measured every 8 h. Maternal laboratory tests, including white blood cell count and C-reactive protein (CRP), were performed on days 1 and 2. Electronic fetal monitoring was applied periodically to detect uterine activity and fetal distress [25]. Biophysical profiles were obtained at admission. Prophylactic antibiotic therapy consisted of amoxicillin (1 mg 3 times a day) plus gentamicin (3 mg/kg/day, given every 8 h). In the case of penicillin allergy, participants received erythromycin (1 mg 2 times a day). A single course of steroids was administered intramuscularly (2 doses of 12 mg β-methasone, 24 h apart).

Randomization

Participants were randomized 36 h after arrival. Randomization proceeded by telephone call to the coordinating centre open 24/7 (Stephanie Moret). The randomization schedule was prepared by a researcher not involved in strategy assignment. Randomization was 1:1 in blocks of four patients, stratified by participating centre. Caregivers and research personnel were not informed of the size of the randomization block.

Interventions

Active management

Women assigned to active management were to give birth 24 h after the second dose of steroids. The mode of delivery – induction or caesarean – was chosen by the attending obstetrician, depending on obstetric considerations. No specific recommendations were given by the research team.

Expectant management

Women assigned to expectant management were admitted to the hospital's antepartum unit. Vital signs were measured every 8 h and white blood cell count and CRP twice a week. Electronic fetal monitoring was performed twice a day and biophysical profiles twice a week. Prolongation of antibiotics after 7 days was left to the discretion of the obstetrician. Expectant management was dropped and delivery expedited if the attending physician noted any of the following: onset of labour, chorioamnionitis, fetal distress, cord prolapse, hematoma, or gestational age ≥34 weeks.

Outcome measures

Newborns were followed throughout their initial stay in the neonatal intensive care unit. The primary outcome measure was a

composite of neonatal death and severe adverse events: cystic periventricular leukomalacia, grade III/IV intraventricular hemorrhage (as defined by Papile [26], proven neonatal sepsis, oxygen requirement at 36 weeks' gestational age, or necrotizing enterocolitis stage > B2 [27]. Cranial ultrasound was performed by qualified neonatologists who routinely test for abnormalities detected during neonatal examinations. All films were interpreted at the coordinating centre by a single experienced neonatologist blinded to intervention group (Olivier Claris).

The secondary outcome measure was clinical chorioamnionitis, defined as maternal antepartum temperature ≥37.8 °C (100.4 °F) and any 2 signs/symptoms: maternal tachycardia (>120 beats/min), maternal leukocytosis (>18,000 cells/mm^3), fetal tachycardia (>160 beats/min), uterine tenderness, and/or purulent or foul-smelling amniotic fluid.

Statistical analysis

Results were analyzed by intention-to-treat and reported as odds ratio (OR) and 95% confidence interval (CI). We used Student's t-tests to compare continuous variables and chi-square tests or Fisher's exact test for categorical variables. Kaplan-Meier curves were constructed for time from randomization to delivery and compared using the log rank test. All analyses were done using SAS version 8.0 (SAS Institute Inc., Cary, NC).

Based on a subset of the DOMINOS study, we estimated neonatal mortality/morbidity as 24% in the expectant management group [23]. Assuming an effect size that shows clinical improvement, i.e. to 12.5% mortality/morbidity, we calculated a sample size of 314, or 157 women in each arm, assuming a Type I error (two-sided) of 0.05 and 80% power. No interim analysis was initially planned.

Results

Participants

After 2 years and despite many efforts to improve recruitment, it became clear that we would not reach target sample size in the time allotted by the funding agency. An interim analysis was conducted and it was decided that those results should be published instead.

We assessed 360 women for eligibility, in 2003–2005. Of these, 78 delivered before the second day of the latency period and 34 were not informed (Fig. 1). Of the remainder, 139 (56%) agreed to participate and were randomized: 69 to the active management group and 70 to the expectant management group.

Baseline characteristics did not differ significantly between randomized and non-randomized women (Supplemental Table S1). However, the use of steroids in randomized women

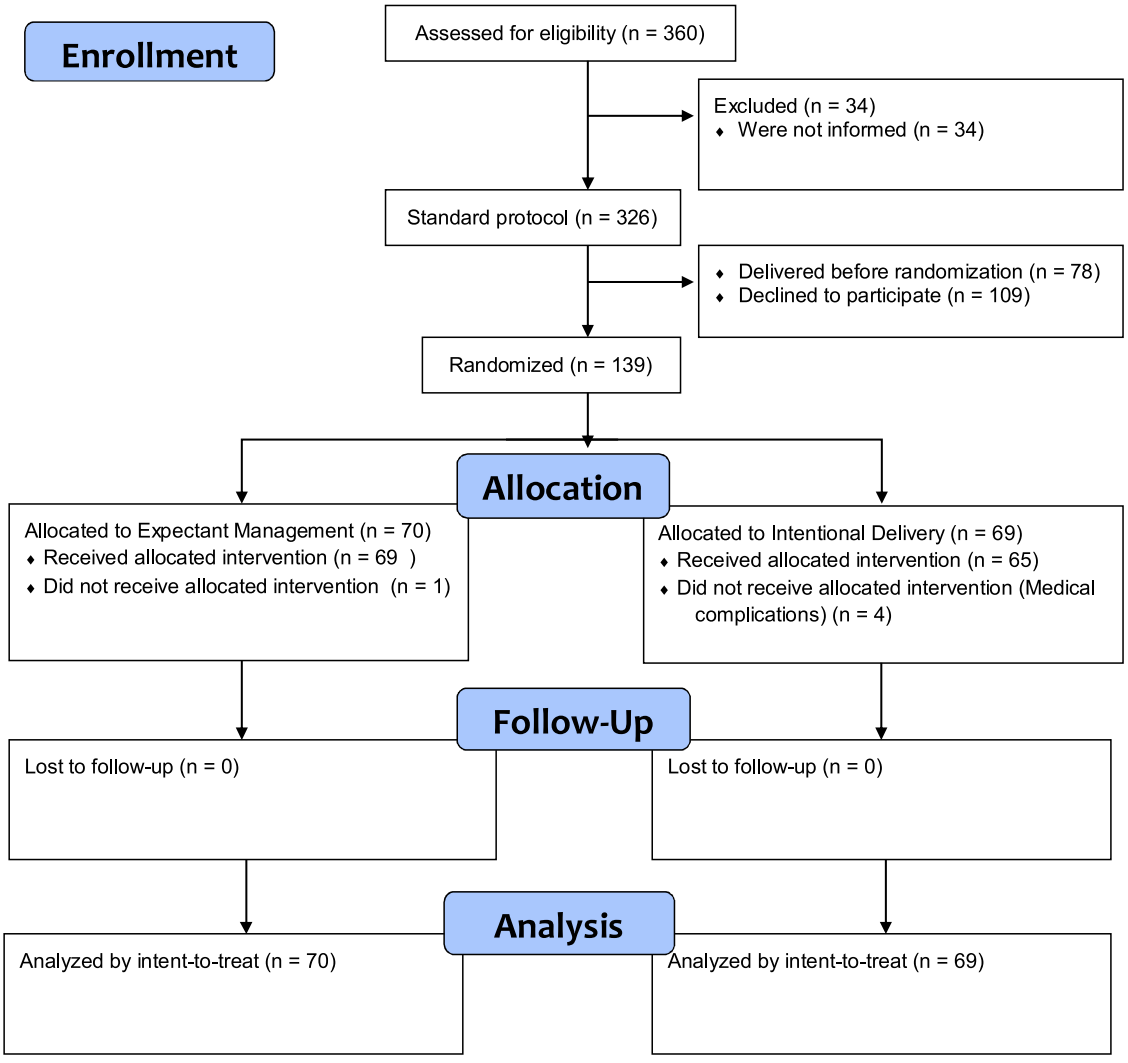

Fig. 1. Participant flow chart.

as compared to non-randomized was lower before rupture (9% of women vs. 22%; $P < 0.01$) and, as per protocol, greater during the latency period between PPROM and delivery (100% vs. 91%, respectively; $P < 0.01$).

At baseline, the intervention and control groups did not differ significantly (Table 1). Mean maternal age was about 30 years. Less than 10% had conceived using assisted reproductive technologies, and for about 40%, this was their first child. Almost all women were covered by universal health insurance, as is the norm in France. Mean gestational age at PPROM was similar (30.0 ± 1.3 for expectant management; 30.2 ± 1.2 for active management). Of note, fully 100% of participants received their antibiotics and steroids. The only significant difference was that, at admission, fewer women in the expectant management group had CRP > 20 mg/L than in the active management group ($P = 0.04$).

Maternal outcomes

Expectant management was associated with a mean latency period between PPROM and delivery of 11.7 ± 9.8 days, as compared to 2.8 ± 0.6 days in the active management group (median 8.4 (1.8–44.2) vs. 2.7 (1.9–4.3) days, respectively). The Kaplan-Meier survival curve for time elapsed between randomization and delivery is shown in Fig. 2. Of the 69 women assigned to the active management group, 65 (94%) gave birth with no complications (Table 2). In the expectant management group, there were 35 cases of medical complications necessitating delivery, including 2 chorioamnionitis and 3 placental abruptions (no chorioamnionitis and one placental abruption in the active management group). Women in active management were more likely to have a caesarean section than those in expectant management (80% vs. 60%, respectively; $P < 0.01$). Most study centres had high rates of caesarean delivery (Supplemental Table S2).

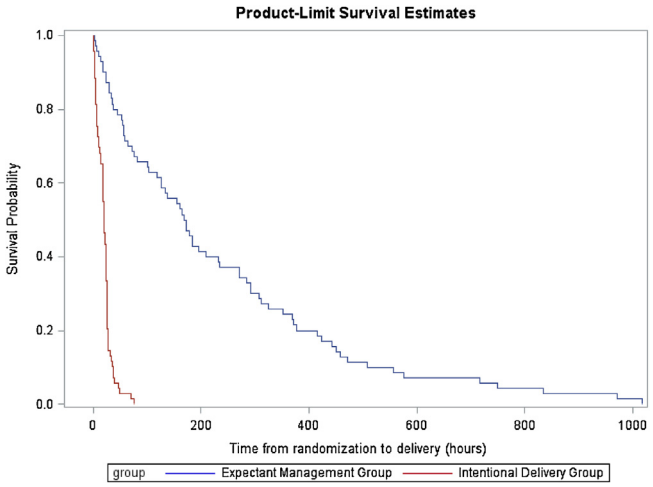

Fig. 2. Kaplan-Myer survival curve showing time elapsed between randomization and childbirth.

Neonatal outcomes

The median gestational age at birth was 31.6 (27.6–34.9) and 30.3 (27.9–32.6) weeks, for expectant management and active management, respectively (Table 3). In the neonatal period, two deaths occurred in the active management group, one of which

Table 1
Participant characteristics.

	Expectant management group (N = 70) n (%)	Active management group (N = 69) n (%)	*P* value
Maternal characteristics			
Maternal age, mean ± SD, years	29.4 ± 5.5	29.9 ± 5.5	0.64
Maternal age, median (min, max), years	29.3 (18.4, 40.1)	29.7 (19.5, 42.8)	
Use of assisted reproductive technologies	4 (6)	3 (4)	1*
Marital status, married or common-law	66 (94)	62 (90)	0.37*
Covered by medical insurance	63 (91)	62 (90)	1
Unemployed	7 (10)	7 (10)	1
Smoking status			0.78
No cigarettes	41 (60)	42 (62)	
1–10 cigarettes/day	19 (28)	16 (23)	
>10 cigarettes/ day	8 (12)	10 (15)	
Nulliparous	22 (31)	28 (41)	0.29
Cervical cerclage	1 (1)	2 (3)	0.62
Gestational age at rupture of membranes, weeks			0.66
$28^{0/7}$–$28^{6/7}$	16 (23)	11 (16)	
$29^{0/7}$–$29^{6/7}$	15 (22)	19 (28)	
$30^{0/7}$–$30^{6/7}$	17 (25)	15 (22)	
$31^{0/7}$–$31^{6/7}$	21 (30)	23 (34)	
Gestational age at rupture, mean ± SD, weeks	30.0 ± 1.3	30.2 ± 1.2	0.35
Median (min, max), weeks	30.1	30.3	
High blood pressure	0	1 (1)	0.50*
Gestational diabetes	0	1 (1)	0.50*
Amniotic fluid index at admission <5	24 (40)	21 (38)	0.85
White blood cell count >15 000/mm^3	11 (16)	14 (21)	0.51
C-reactive protein > 20 mg/L	3 (4)	10 (15)	0.04
Steroids administered before rupture of membranes	8 (11)	4 (6)	0.37
Treatment during latency period between membrane rupture and delivery			
Antibiotics	70 (100)	69 (100)	1
Tocolytics	39 (56)	47 (68)	0.16
Corticosteroids	70 (100)	69 (100)	1

Percentages are based on the total number of answers received.
* *P* values using Fischer's exact test.

Table 2
Delivery.

	Expectant management group (N = 70) n (%)	Active management group (N = 69) n (%)	*P* value
Reasons for delivery			<0.0001
Intentional delivery	1 (1)	65 (94)	
Spontaneous onset of labour	25 (36)	0	
Medical or suspected complications	35 (50)	4 (6)	
Chorioamnionitis	2 (3)	0	0.50
Placental abruption	3 (4)	1 (1)	0.62
Non-reassuring fetal heart rate tracings	11 (16)	1 (1)	0.007
High blood pressure	0	1 (1)	1
Suspected complications	19 (27)	1 (1)	<0.0001
Elevated markers (C-reactive protein, white blood count)	13/19 (68)		
Elevated bacterial counts (vaginal swab, amniocentesis)	2/19 (11)		
Contractions < 1 per 20 min	8/19 (42)		
Change in amniotic fluid colour	8/19 (42)		
Suspected acute fetal distress	5/19 (26)		
Reached 34 weeks' gestation, delivery as per protocol	9 (13)	0	
Latency between PPROM and delivery			<0.0001
<4 days	19 (27)	67 (97)	
4–6 days	6 (9)	2 (3)	
7–13 days	21 (30)	0 (0)	
>14 days	24 (34)	0 (0)	
Mean latency ± SD, days	11.7 ± 9.8	2.8 ± 0.6	<0.0001
Median latency (range), days	8.4 (1.8-44.2)	2.7 (1.9-4.3)	
Non-vertex presentation	25 (36)	17 (25)	0.15
Caesarean delivery	42 (60)	55 (80)	<0.01

Table 3
Neonatal outcomes.

	Expectant management group (N = 70) n (%)	Active management group (N = 69) n (%)	*P* value
Male sex	40 (57)	38 (55)	0.81
Birth weight, mean ± SD, gm	1664 ± 386	1504 ± 272	0.006
APGAR score < 7	5 (7)	3 (4)	0.72
Gestational age at birth			0.01
28 weeks	6 (9)	11 (16)	
29 weeks	11 (16)	17 (25)	
30 weeks	8 (11)	16 (23)	
31 weeks	21 (30)	18 (26)	
32 weeks	16 (23)	7 (10)	
33 weeks	4 (6)	0	
34 weeks	4 (6)	0	
Mean gestational age ± SD, weeks	31.3 ± 1.6	30.3 ± 1.3	<0.0001
Median gestational age (range), weeks	31.6 (27.6-34.9)	30.3 (27.9-32.6)	
Mortality			
Death[a]	1 (1)	2 (3)[b]	0.62
Serious adverse events			
Clinical signs of respiratory distress	39 (56)	45 (65)	0.25
Low blood pressure requiring treatment	6 (8)	9 (13)	0.40
Anemia requiring transfusion	10 (14)	9 (13)	0.83
Symptomatic patent ductus arteriosus	1 (1)	1 (1)	1
Oxygen requirement at 36 weeks[a]	2 (3)	2 (3)	1
Intraventricular hemorrhage III-IV [a]	0	0	
Leukomalacia[a]	4 (6)	1 (1)	0.36
Necrotizing enterocolitis[a]	3 (4)	1 (1)	0.62
Sepsis[a]	1 (1)[c]	3 (4)[d]	0.36
Length of hospital stay Mean ± SD, days	39.7 ± 2.77	47.0 ± 1.69	<0.03
Length of stay, days Median (min, max)	36 (1, 142)	46 (23, 87)	
Combined neonatal mortality/morbidity outcome	9 (12.9)	9 (13.0)	0.97

[a] Included in combined neonatal mortality and morbidity outcome (last line of table).
[b] One death due to a heart malformation.
[c] Gram-negative sepsis observed on neonatal day 1.
[d] One sepsis case on day 9, due to coagulase-negative staphylococcus; 2 cases on neonatal days 29 and 34, respectively, due to Streptococcus bovis. CRP < 4 in all cases.

was associated with a heart malformation. One baby died in the expectant management group. Two infants in each group required oxygen at 36 weeks. There were no cases of intraventricular hemorrhage. The expectant management group had more cystic periventricular leukomalacia and necrotizing enterocolitis than the active management group (4 and 3 vs. 1 and 1, respectively), but these differences were not statistically significant. The combined neonatal death/severe adverse events measure was

12.9% for expectant management and 13.0% for active management (OR 0.98; 95% CI: 0.33–2.93, $P = 0.97$).

Beyond gestational age and birth weight, there were no significant differences between groups, except that the median length of stay was about one week longer in the active management group. At lower gestational ages, there were also more cases of neonatal respiratory distress, but the difference was non-significant. There were 4 sepsis cases altogether, detailed in Table 3.

Comment

In this multicentre randomized controlled trial, we compared two management strategies for women with PPROM at 28–32 weeks' gestation. Expectant management is generally favoured because it allows the fetus to further mature in utero [11]. However, this might be counterbalanced by the risk of antenatal and neonatal complications associated with the latency period. We showed that in a sample of 139 singleton births, as expected, active management resulted in younger gestational ages and lower birth weights, and higher rates of caesarean delivery, as compared to expectant management. However, the combined neonatal death/severe adverse events as well as the rate of chorioamnionitis did not differ significantly between groups. We have to underline that the study was underpowered, as we did not reach target sample size. Nonetheless, MICADO is the largest, if not the only, randomized controlled trial to date focusing on very preterm birth with contemporary management such as antibiotics and corticosteroids, thus contributing important information to advance knowledge in this field.

A 2017 Cochrane study of 3617 women with PPROM at all gestational ages <37 weeks combined [20], identified no clear differences in neonatal sepsis and overall perinatal mortality between active management and expectant management. However, early birth increased the incidence of respiratory distress and caesarean sections. The authors suggested subgroup analyses for research and watchful waiting for delivery. For PPROM at late preterm (34–37 weeks), a 2018 meta-analysis of 3 studies found that the composite neonatal outcome measure was similar for both strategies (8.3% for expectant management group vs. 9.6% for immediate delivery) [28]. Ours was 13% for both groups, a result comparable but understandably higher, as we were investigating very preterm birth. Their neonatal sepsis rates were also similar for both groups.

For PPROM at 28–34 weeks' gestation, only 5 RCTs were published comparing active management and expectant management. All were underpowered and none of them used steroids and antibiotics during latency, as currently recommended [29]. A 2013 meta-analysis of these 5 RCT found that the rates of neonatal sepsis and respiratory distress syndrome were similar in both strategies [30]. Neonatal death was significantly higher with active management and without antenatal steroids. In fact, data on active management for young gestational ages are scarce and require caution in drawing conclusions.

Our secondary outcome was the incidence of clinical chorioamnionitis. In two meta-analyses of PPROM < 37 weeks' gestation and at late preterm, women in active management were less likely to have chorioamnionitis; however, a meta-analysis at PPROM < 34 weeks' gestation found no difference. It is noteworthy that chorioamnionitis incidence is a non robust clinical finding that varies according to factors such as disease definition and associated treatments [10,31]. In Mercer's 1993 study, the rate of chorioamnionitis was 28% for expectant management vs. 11% for active management [15]. In 2005 with antibiotic and antenatal steroid therapies, Lieman et al. found a 21% incidence of clinical chorioamnionitis for PPROM at 28–32 weeks' gestation [18]. Our low rates (2 cases only) may result from several factors. First, modern management included prophylactic antibiotics from PPROM to birth. Combined therapy included ampicillin and gentamicin instead of erythromycin which was associated with an increase of early neonatal sepsis. Second, contamination bias may have been present in the expectant management group in that physicians accustomed to active management may not have waited for clinical chorioamnionitis criteria before deciding to deliver. Although few centres in France used an early delivery strategy at the time, obstetricians participating in this study would have been exposed de facto, through their patients randomized to the active management group. Contamination bias would therefore have been linked not to existing practice in France, but to participation in the study itself. Third, patients were monitored using CRP levels. Lastly, there was a delay of 48 h with antibiotics and steroids before randomization (selection bias).

Importantly, according to a recent meta-analysis, only histological rather than clinical chorioamnionitis is a risk factor for neurological outcomes such as cerebral palsy. This information is not available in our study but the PPROMEXIL trial showed that active management reduced the risk of histological chorioamnionitis and therefore could protect against cerebral palsy [36,37]. Further, our team has worked on an animal model to explore the link between duration of exposure to inflammation and neurological outcomes. We showed that neurological deterioration was associated with a longer duration of intrauterine exposure to inflammation [38].

The latency period in our sample was increased by almost a week by expectant management as compared to active management (median 8.4 days (range 1.8–44.2) vs. 2.7 days (1.9–4.3), respectively). This confirms previous research that about half of births occur within a week of PPROM [32].

Our rate of caesarean delivery was high (60% and 80%), and as reported by most researchers, greater in the active management group than in expectant management [20,28,30]. Our rate is also consistent with a 2016 report of a 2011 population-based prospective cohort in France of 702 singletons born at 24–32 weeks' gestation (EPIPAGE 2 study) reporting a 53% C-section rate after PPROM [33]. The elevated rate of C-sections in PPROM, evaluated at 43.7% in a 2012 study by Mousiolis et al., may be attributable to breech presentations (36% and 25% in our study) and to perceived benefits of C-section in births below 30 weeks' gestation [34].

In future endeavours, perhaps a paradigm shift is in order, to consider PPROM as a complex syndrome rather than a single entity [39]. This would allow a classification of patients by presenting phenotype, with neonatal outcomes as the primary consideration rather than extension of pregnancy alone [40–43]. Using innovative technologies, a search for novel biomarkers in amniotic fluid obtained vaginally or by amniocentesis may personalize delivery strategies for optimal neonatal outcomes and healthier children [44].

This study has several limitations, one of which was sample size. An interim analysis showed that our results would not have been different had we continued. Further, although many women refused to participate in research under stressful life situations, there were no significant baseline differences between participants and non-participants. This result is concordant with the study of Kasenda et al. who found that the most frequent reason for discontinuation of RCT was poor recruitment [35]. A second limitation is that the study was conducted a few years ago. The only difference in management is that magnesium sulfate is now added for neuroprotection; more specifically, for the prevention of cerebral palsy, which was not measured in this study [11]. Importantly, a major strength of MICADO is that it was a randomized controlled trial with an intent-to-treat analysis. Another is the quasi-universal health coverage in France that helps standardize antenatal follow-up for all women, including those at our participating centres.

Perspectives

This superiority trial showed no clear differences between expectant management to 34 weeks and active management. However, the target sample size not having been reached, the study was underpowered to draw firm and reliable conclusions. Nonetheless, our results are useful for future research and meta-analyses on the optimal strategy of care in patients with PPROM.

To our knowledge, MICADO is the only study and the largest RCT to date addressing delivery options for PPROM at 28–32 weeks' gestation, i.e. at very preterm birth, wherein the high mortality of extremely preterm birth is eliminated and the risk of major neurodevelopmental complications remains considerable.

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Appendix A. Supplementary data

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