Conservative management of preterm premature rupture of membranes < 30 weeks of gestational age: Effectiveness of clinical guidelines implementation strategies

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ABSTRACT

Objective: To compare obstetrical and neonatal outcomes in patients with p-PROM (preterm premature rupture of membranes) at less than 30 weeks of gestational age before and after the application of protocols developed on the basis of international guidelines and to identify local barriers and strategies for their implementation.

Study design: Single and twin pregnancies with p-PROM < 30 weeks of gestation without signs of infection were retrospectively collected. The population was divided in two groups. Group A contained patients treated before the introduction of the protocol, hospitalized from the day of the p-PROM to delivery and treated according to clinicians' practice. Group B included patients managed according to a standardized protocol, treated with home care management under strict surveillance, after 48 h of hospitalization.

Results: 19 women with 21 newborns in group A and 22 women with 26 newborns in group B were enrolled. Maternal characteristics and p-PROM gestational age were comparable. In group A we observed minor latency time from diagnosis to delivery (1.6 vs 6.5 weeks, $p < 0.001$) with lower gestational age at delivery (25.8 ± 2 vs 30.7 ± 4.2 weeks, $p = 0.00$) and lower newborn weight (859 ± 268 vs 1511 ± 917 g, $p = 0.002$). Concerning neonatal outcomes, in group A there were lower Apgar score at 1 min (4.0 ± 2.1vs 6.3 ± 2, $p = 004$), longer hospitalization (42 ± 38 vs 68 ± 38 days, $p = 0.05$) and, even if non statistically significant, major rate of neonatal mortality ($11,5\%$ vs 19%, $p = 1.00$) and of neonatal complications (need of neonatal intensive care unit, sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, mechanical ventilation). Postnatal follow-up showed comparable outcomes at 24 months of correct age.

Conclusions: Educational and interdisciplinary meetings, along with group performance audit and standardization of procedures are successful strategies to implement guidelines application. Applying this strategy, we developed a protocol according to international guidelines for the treatment of early onset p-PROM based on a standardized conservative management at home, achieving better results compared to hospital management in terms of latency, gestational age at delivery, neonatal weight and neonatal hospitalization.

Introduction

Preterm premature rupture of amniotic membranes (p-PROM) complicates 2%−3% of pregnancies before 37 weeks of gestation and less than 1% before 34 weeks of gestation. It accounts for about a third of preterm deliveries [1,2]. p-PROM is associated with high neonatal mortality and severe short- and long-term postnatal morbidity. Despite the survival rate of premature infants has increased markedly in recent years due to the improvement in neonatal intensive care, the long-term morbidity remains high [3,4]. The application of defined protocols could have an impact on the effects of extreme prematurity by prolonging the gestational age at delivery. Recent meta-analyses and randomized controlled trials recommend conservative management up to at least 34 weeks of gestation to limit the effects associated with prematurity [5]. To achieve this gestational age, current guidelines suggest broad-spectrum antibiotic therapy initially intravenously and subsequently orally to reduce the rate of maternal and neonatal infections, magnesium sulfate for neuroprotection if delivery is planned or estimated within 24 h for gestational ages < 32 weeks, a course of corticosteroids to promote lung maturity along with tocolytic therapy only in order to complete the aforementioned cycle [6–10]. Recently some guidelines, such as the French College of Gynecologys and Obstetricians (CNGOF) ones, suggest conservative management at home in cases of clinical stability after 48 h of hospitalization, with accurate clinical, laboratory and ultrasound monitoring [10–12]. Guidelines' application, however, is often slow, complex and sometimes partial due to factors related mainly to their applicability in the context in which they must be introduced.

The objective of this study was to compare the clinical course of pregnancy and neonatal outcomes in patients with p-PROM occurring before 30 weeks of gestation before and after the application of the protocol developed starting from international guidelines.

Materials and methods

Design of the study

Retrospective study on pregnancies complicated by p-PROM occurring before 30 weeks' gestation. Data were collected in the General Regional Hospital "F. Miulli" in Italy from 2011 to 2020. In 2016 a protocol based on international guidelines [6,8–10] on p-PROM was introduced. All singleton and twin pregnancies with p-PROM < 30 weeks without clinical or laboratory signs of infection were included. The exclusion criteria were delivery within 48 h of premature preterm rupture of membranes, fetal and uterine malformations, delivery in another hospital.

Management

p-PROM diagnosis was made clinically (amniotic fluid discharge on speculum inspection) and/or with a qualitative immunoassay vaginal test (AmniSure PROM Test, AmniSure International LLC, USA). The population was divided in two groups: group A patients treated before the introduction of the protocol and group B including patients treated according to the standardized protocol. In group A patients were hospitalized from the day of the p-PROM to delivery and they received broad-spectrum antibiotic therapy according to clinicians' practice (ampicillin, cefazoline or macrolide in not standardized posology) and underwent clinical, ultrasound and blood monitoring with repetition of daily inflammation indices and complete vaginal and cervical swabs with antibiotic sensitivity (eventually a specific therapy if not covered from broad spectrum therapy).

In group B patients were treated according to a standardized protocol and with home care management after 48 h of hospitalization.

The protocol included: intravenous antibiotic therapy for 48 h with ampicillin (2 g every 6 h) and erythromycin (250 mg every 6 h);

ultrasound evaluation with assessment of amniotic fluid, fetal presentation, placental insertion, fetal biometry with fetal weight estimation, detailed anomaly scan and cervical length measurement; complete cervical and vaginal swabs with antibiotic sensitivity (eventually a specific therapy if not covered from broad spectrum therapy) and vaginal-rectal swab for the search of group B Streptococcus infection; urine culture; blood tests including complete blood count, C-reactive protein (CRP), procalcitonin, liver and kidney function tests, and coagulation tests. During hospitalization, clinical monitoring with measurement of the maternal heart rate and temperature every 4 h, blood exams with daily repetition of inflammation indices and ultrasound check (daily evaluation of the fetal heart rate, amniotic fluid assessment and fetal Doppler velocimetry after 48 h if patient was eligible for home management and every 72 h if she continued hospitalization) were performed.

In case of abnormal results the patient was not discharged home but continued in-hospital clinical monitoring and intravenous antibiotics.

After 48 h, in the absence of signs of infection or uterine contractility, the patient was discharged with indications for oral antibiotic therapy (amoxicillin 250 mg every 8 h and erythromycin 250 mg every 8 h) for 5 days and daily check of the body temperature and evaluation of any changes in vaginal discharge. The patients had blood counts and inflammation indices checked twice a week and obstetric check-up in the high-risk outpatient clinic approximately every 7 days (clinical, ultrasound and cardiotocography if > 30 weeks' gestation). In case of signs of infection (malodorous vaginal discharge, abnormal inflammation indexes such as WBC > 18,000 and CRP > 2 mg/dl being considered significant) they were subjected to a new antibiotic cycle at home (amoxicillin 250 mg every 8 h and erythromycin 250 mg every 8 h per os or, if vaginal and cervical swab positive according to their antibiotic sensitivity) and, if not resolved, hospitalized. In case of hyperpyrexia, defined as body temperature > 38 °C, alone or associated to other signs of infections the patient was hospitalized. All patients were managed at home until the onset of spontaneous labor, signs of chorioamnionitis (defined as the presence of hyperpyrexia plus at least one factor among increased inflammation indices, uterine activity, fetal tachycardia, maternal tachycardia, level 3 meconium-stained fluid), fetal heart rate abnormalities or acute complications (placental abruption, cord prolapse). At the 34th week of gestation, in the absence of any of these signs, an indication for delivery was given (either induction of labor or elective cesarean section based on patient's history).

Corticosteroid prophylaxis was performed in both groups (two intramuscular doses of 12 mg of betamethasone 24 h apart) starting from 23 weeks [13]. In case of uterine activity, atosiban as tocolytic therapy was administered in order to complete the course of corticosteroids. If signs of chorioamnionitis were detected the tocolytic therapy was stopped. Magnesium sulfate was administered intravenously for neuroprotection for gestational ages < 32 weeks.

Outcomes

The following maternal demographic data were collected: maternal age, parity, history of previous p-PROM or preterm deliveries, spontaneous pregnancy or pregnancy obtained with assisted reproduction techniques (ART), previous cesarean section, cervical cerclage and the presence of any comorbidities (i.e. gestational diabetes, thyroid disease, hypertensive disorders, hematological diseases).

The obstetric outcomes included: length of maternal hospitalization (in the intervention group obtained by the sum of the days of repeated hospitalizations); gestational age at delivery; the duration of latency defined by the time interval between the p-PROM and delivery; mode of delivery and obstetric complications such as placental abruption and cord prolapse. Along with birth weight, gestational age at delivery, and 1- and 5-minute Apgar score, neonatal outcomes included: neonatal mortality (defined as mortality in the first 28 days of life), neonatal intensive care unit (NICU) admission, length of hospitalization, neonatal

Table 1
Maternal characteristics and pregnancy outcomes.

	Group A (n19)	Group B (n22)	p value
Age (y)	36 ± 5	36 ± 6	0.979
Nulliparous (%)	9 (47,3%)	12 (54,5%)	0.300
Twin pregnancy (%)	2 (11%)	4 (15,4%)	0.540
Assisted reproductive technique (%)	3 (15,7%)	5 (23%)	0.703
History of preterm delivery (%)	3 (15,7%)	3 (13,6%)	0.999
Presence of cerclage (%)	1 (5,3%)	1 (4,5%)	0.990
Gestational diabetes (%)	4 (21%)	5 (23%)	0.999
Hypertension (%)	1 (5,3%)	1 (4,5%)	0.999
Cholestasis (%)	0	1 (4,5%)	0.999
Thyroid disease (%)	4 (21%)	4 (18%)	0.999
p-PROM (weeks)	24.0 ± 2.3	24.2 ± 4	0.774
Hospitalization of the mother (days)	16 ± 7	13 ± 8	0.138
Cesarean section (%)	13(68%)	18(82%)	0.469

p-PROM, preterm premature rupture of membranes

Table 2
Neonatal outcomes according to the two different groups.

	Group 1(n. 21)	Group 2(n. 26)	p value
Gestational age at delivery (weeks)	25.8 ± 2	30.7 ± 4.2	0.000[**]
Neonatal weight (grams)	859 ± 268	1511 ± 917	0002[**]
Apgar 1 min (score)	4.0 ± 2.1	6.3 ± 2	0.004[**]
Apgar 5 min (score)	7.5 ± 1.4	7.8 ± 1.4	0.372
NICU admission (%)	19 (90.5%)	20 (76.9%)	0.259
Invasive respiratory support (%)	15 (71.4%)	15 (57.7)	0.330
Sepsis (%)	9 (42.8%)	9 (34.6%)	0.563
Necrotizing enterocolitis (%)	2 (9.5%)	2 (7.7%)	0.999
Retinopathy of prematurity (%)	10 (47.6%)	5(19.2%)	0.038[**]
Bronchopulmonary dysplasia (all grades)l (%)	8 (38%)	5 (19.2%)	0.151
IVH ≥ second stage (%)	2 (9.5%)	3 (11.5%)	0.999
Neonatal mortality (%)	4 (19%)	3 (11.5%)	1.000
Neonatal hospitalization (days)	68 ± 38	42 ± 38	0.050[**]

NICU, neonatal intensive care unit; IVH, intraventricular hemorrhage;
[**] $p < 0,05$

sepsis (defined as sepsis in an infant with a positive blood culture), need for invasive ventilation during hospitalization, bronchopulmonary dysplasia (BPD- oxygen requirement at 36 weeks' gestation), grade 3 intraventricular and/or periventricular hemorrhage (IVH), surgical necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP). Post-natal follow-up at 24 months of correct age was performed by the same hospital with neurodevelopmental evaluation for the identification of major disabilities (cerebral palsy, cognitive impairment, bilateral visual deficit < 1/10, permanent hearing impairment) and minor disabilities (regulation disorders, motor and postural sphere disorders, learning difficulties, pathologies of adaptive functions), evaluation of visual and auditory functions and of any respiratory and cardiovascular outcomes.

Statistical analysis

Numerical data were expressed as mean± standard deviation. Categorical variables were reported as absolute frequency and percentage. Comparisons between groups were made by Student's t test or Mann-Whitney nonparametric test when the continuous variable showed a non-normal distribution evaluated by Shapiro-Wilk test. Categorical variables were tested between groups using the chi-square test or Fisher's exact test in the case of expected frequency less than 5 in at least one cell of the two-by-two table (categorical variable group). A p < 0.05 was considered statistically significant.

Results

A total number of 41 pregnancies including 47 newborns were collected. The cases were distributed as follows: 19 pregnancies in group A (17 singleton and 2 twin pregnancies) and 22 pregnancies in group B (18 singleton and 4 twin pregnancies) for a total of 21 newborns in the first and 26 newborns in the second. Maternal demographic characteristics and obstetric history are illustrated in Table 1: rate of previous preterm delivery (15.7 vs 13.6%), maternal comorbidity (gestational diabetes, hypertension, cholestasis and thyroid disease), gestational age of p-PROM (24.0 +/−2.3 vs 24.2) and cesarean section rate (68 vs 82%) were comparable. In group A 13 women underwent cesarean section, 6 vaginal delivery; in group B 18 women underwent cesarean section and 4 vaginal delivery. Indications for cesarean section were in the two groups: non cephalix presentations (8 patients), previous cesarean section or uterine surgery (8 patients), placenta previa (1 patient), placenta abruption (5 patients), iperpirexia and clinical signs of chorioamniotitis (6 patients) and fetal Doppler alterations (3 patients).

In group B 4 patients needed rehospitalization: 1 for risk of premature delivery and 3 to undergo intravenous antibiotic therapy.
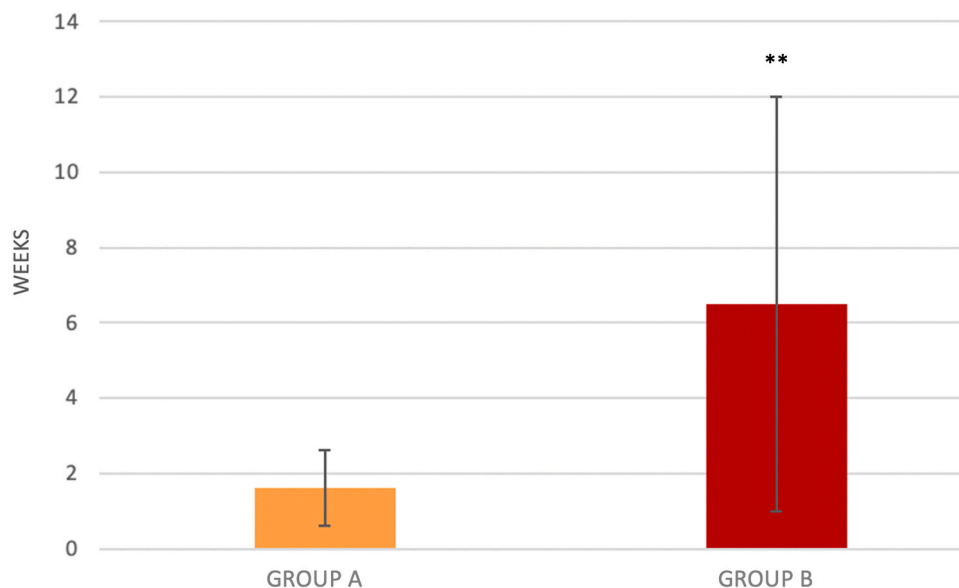

Fig. 1. Latency to delivery, expressed in weeks, in group A (without protocol) and in group B (after application of the protocol) * * p < 0.05.
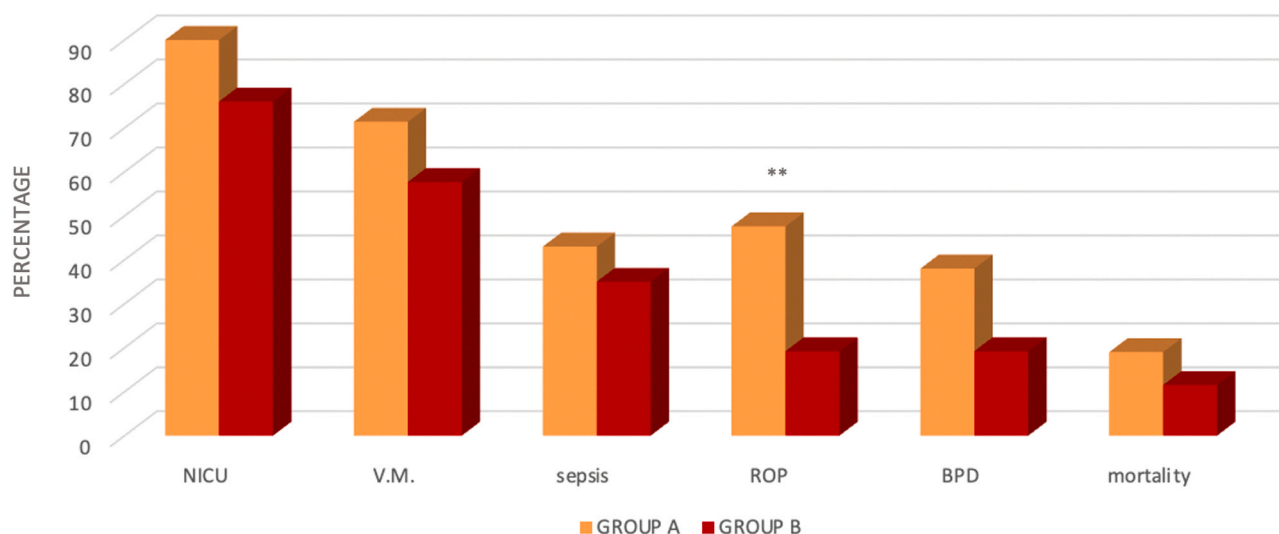
Fig. 2. Main neonatal outcomes, expressed in percentage, in group A(without protocol) and B (treatment according to protocol). NICU: neonatal intensive care unit, M.V. mechanical ventilation, ROP: retinopathy of prematurity (all grades), BPD: bronchodysplasia (all grades). ** p < 0.05.

Regarding obstetric complications that indicated delivery: placental abruption was reported in two patients in group A (10.5%) and three patients in group B (18%), three patients in both groups showed clinical signs of chorioamnionitis (15.7% and 13.6%, respectively) and one patient in group B had a placenta previa. The other indications for delivery were unstoppable labor and fetal growth restriction with abnormal doppler. Induction of labor was performed in four patients in group B at 34 weeks as most guidelines suggest. No complications were observed in the post-partum in both groups.

The mean gestational age at delivery and, consequently, the latency time between membrane rupture and delivery were significantly lower in group A than in group B with a gestational age at delivery of 25.8 vs 30.7 weeks (p < 0.001) and latency of 1.6 vs 6.5 weeks (p < 0.001), respectively (Fig. 1 and Table 2).

Significant differences between the two groups were also seen regarding perinatal outcomes (Table 2): the Apgar score at 1 min was 4 in group A vs 6.3 in group B (p = 0.004), the birth weight was 859 ± 268 g and 1511 ± 917 g, respectively (p = 0.002). A difference in neonatal mortality was observed (4 in group A- 19% vs −3 in group B- 11.5%) but did not reach statistical significance (p = 1.00). The newborns in group A had a longer hospitalization (68 days vs 42 days, p = 0.05) and a higher rate of neonatal complications even if the difference does not appear to be statistically significant apart from the occurrence of ROP (p = 0.038).

All newborns were enrolled in the multidisciplinary follow-up program at the corrected age of two years. 16 of the 17 children discharged in group A and all 23 newborns in group B completed the follow-up. The mean follow-up evaluation age was the same in the two groups (24.4 ± 1.5 months in group 1 vs 23.8 ± 1.7 months in group 2). No major disability was observed in neither of the two groups. Two children in group A and one child in group B had a minor disability mainly in the spectrum of regulation disorders. One child in group A with postnatal severe BPD required home oxygen therapy.

Discussion

The main finding of this study was that the application of standardized guidelines led to a significant increase in latency time, gestational age at delivery and birth weight. As a consequence, the length of NICU hospitalization was significantly shorter in group B, with clear advantages for mother-child relationship and for cost-effectiveness policies. Early neonatal outcomes were also influenced by the increased mean gestational age at delivery and birth weight obtained in group B, which had a lower prevalence of prematurity related morbidities.

The results obtained are the conclusion of a process that led to the correct application of international guidelines on the p-PROM management. The guidelines are considered essential for health policy and for the improvement of the quality of health care. Despite this, they are not always applied and included in clinical practice due to a set of factors depending on the characteristics of the guidelines themselves, on the clinical context and on the healthcare personnel that should apply them. It is therefore crucial to identify the aforementioned limiting factors and to choose the most correct strategies to overcome them and encourage the introduction and dissemination of the guidelines [14].

There are several meta-analyses in the literature in this regard [15, 16]. Fischer et al. differentiates the critical issues into personal factors related to lack of knowledge and incorrect attitude of the staff, factors related to the drafting of the guidelines such as low scientific evidence, poor applicability, excessive complexity, and external factors such as lack of organizational, economic, human resources, time, poor collaboration with other specialists [17]. During our study, after an internal survey among gynecologists, midwifes and neonatologists, focused on the whole management of p-prom, external and staff-related criticalities emerged: poor guidelines knowledge, lack of motivation, poor organization in the management of new practices, insufficient culture of learning, difficulty in collaborating with other professional figures such as neonatologists and midwives and the lack of a standardized protocol Fig. 2.

The strategies implemented were first of all the creation and dissemination of an internal protocol born from a careful analysis and contextualization of the available guidelines, followed by the training of obstetric and pediatric staff through multidisciplinary work groups.

Another fundamental strategy was the introduction of periodic multidisciplinary audits on single cases with the aims of interaction, comparison and learning. Of great importance was the creation of an outpatient clinic managed by obstetric pathology specialists which made it possible to unify and standardize the management of patients with p-PROM. Furthermore, a very precise division of roles was defined with the identification of a local leader who was intended to coordinate the work, driving the force in terms of motivation and training for the implementation of the guidelines [15–17]. Finally, the introduction of an accurate counseling carried out by the obstetrician and the neonatologist on the benefits and risks associated with the different

therapeutic attitudes in case of p-PROM was fundamental in order to overcome the fear of the patients. The aforementioned strategies have proven efficacy in implementing the guidelines as demonstrated by the good maternal and neonatal outcomes obtained.

The data are in line with studies comparing conservative management in hospital and at home in the literature. A Cochrane review including only two randomized controlled trials with an overall number of 116 women, concluded that home management is related to shorter hospitalization and lower costs but does not reach conclusions regarding maternal and neonatal outcomes [18]. The most recent retrospective studies describe home management as a real option for p-PROM guaranteeing excellent results in terms of prevention of prematurity and maternal and neonatal outcomes [19,20]. The increased latency period is clearly the main benefit of home management and has been shown by other studies [2,11,21]. In fact, as can be deduced from the EPIPAGE 2 study and from a recent study by Baser et al., the increase in latency does not worsen the neonatal prognosis but rather leads to fewer complications [22,23]. The main limitations of the study are related to the small sample size and retrospective design which may have affected the statistical robustness. However, it also has several strengths. First of all, since the mean gestational age of membrane rupture is several weeks lower than that of previous studies [2,11,12,19,21], our results show that conservative management at home is also applicable to early gestational ages with good results. Furthermore, the analysis of the limitations and strategies to implement the use of the guidelines offers an important starting point for reflection and application in the most diverse contexts.

Conclusions

Training interventions, audits, multi-professional and multidisciplinary counseling represent successful strategies for the implementation of the guidelines. In our study, they allowed the implementation of a standardized conservative management of p-PROMs at home, even at very early gestational ages, offering better results in terms of latency, gestational age at delivery and neonatal weight with a possible economic advantage and patient satisfaction. Further multicenter studies, with larger sample size, are necessary to confirm the data obtained.

Declaration of Competing Interest

All the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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