EXPECTANT CONDUCT IN PREMATURE RUPTURE OF AMNIOTIC MEMBRANES IN LATE PRETERM INFANT: EXPERIENCE IN TERTIARY UNIT

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ABSTRACT

INTRODUCTION: maternal-fetal complications such as corioamnionitis and neonatal death, triggered by premature rupture of preterm ovular membranes (PPROM), caused many societies to adopt expectant management up to 34 weeks. However, currently, weight societies in the obstetric world have reviewed such conduct.

OBJECTIVE: this study aims to describe obstetric and perinatal morbidity in expectant management in patients with PPROM with GA between 34 and 36 weeks and 6 days, admitted to a tertiary hospital unit, a reference for the care of high-risk pregnancies in the state of Goiás.

METHOD: this is a descriptive retrospective observational study, in which women with single pregnancy were included, presenting PPROM confirmed between 34 ± and 36 + 6 weeks of gestation and who were not in labor within 24 hours after rupture of membranes. Result: the present study evaluated 94 patients, and 4.3% (4/94) of chorioamnionitis was observed; 1% (1/94) of puerperal infection; 3.2% (3/94) of Apgar < 7 in the 5th minute; 11.7% (11/94) of admission of newborns in the ICU and 0% (0/94) of neonatal death.

CONCLUSION: women with late PPROM, expectant management, as well as immediate delivery, are acceptable alternatives, given the equivalence in the literature in relation to the advantages and disadvantages for the maternal-fetal binomial.

KEYWORDS: PREMATURE, FETAL MEMBRANES, WATCHFUL WAITING

INTRODUCTION

Premature Rupture of Ovule Membranes (PROM) is the spontaneous rupture of the ovular and amniotic membranes that is known to occur before the onset of labor. This definition is independent of gestational age. Thus, one can find cases of PROM before 37 weeks of gestation (preterm premature rupture of the ovular membranes - PPROM) and at term (after 37 weeks). The latency period is defined as the interval between the rupture of the membranes and the beginning of labor[1].

It is known that when preterm ovular membranes are ruptured, the latency period is inversely proportional to gestational age. In term fetuses, when the membrane ruptures, a large part evolves to childbirth within 24 hours[1].

PPROM complicates about 1-5% of all pregnancies and accounts for 30-40% of all preterm births. It is associated with an increase in maternal and fetal mortality.[2] The United States of America is responsible for about a third (32.6%) of all premature births[3] and for approximately one fifth (18.2%) of premature births in Brazil, being, perhaps, the maternal complication most common of prematurity in the Brazilian panorama[4].

The etiology of spontaneous PROM is complex and multifactorial and involves factors that change the structure of membranes, whose main component is collagen, the most important being: Uterine overdistension (polyhydramnios and multiple gestation), mechanical factors (uterine contractions and fetal movement), alteration of cervical integrity (isthmus cervical incompetence and cerclage), intrinsic membrane factors (alpha-1-antitrypsin deficiency and Ehlers-Danlos syndrome) and alteration of tissue oxygenation (smoking). These factors are related to ascending infection of the vaginal flora, which is the most frequently identifiable cause associated with PROM[1].

As for neonatal complications, they come mainly from prematurity. In preterm births, the most prominent complication is respiratory distress syndrome, accounting for 63.63% of morbidity and 53.3% of mortality in a study of 100 cases of patients with ruptured membranes between

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28 and 37 weeks[5] .

As for maternal complications, 30% of patients with ruptured membranes between 24 and 37 weeks develop chorioamnionitis[6]. Its incidence is higher the lower the gestational age, with 41% in children under 27 weeks, 15% between 27 and 37 weeks and 2% over 37 weeks[7]. As for placental abruption, an incidence of 2.29% is observed, compared to a rate of 0.86% among women with intact membranes[8].

The diagnosis of PROM is essentially clinical, based on anamnesis and physical examination 90% of the time. In history, the typical complaint will be the sudden loss of liquid through the vagina, with a peculiar smell and appearance, in moderate quantity, which wets the patient's clothes. Specular examination reveals spontaneous loss of fluid through the external orifice of the uterine cervix and/or collected in the cul-de-sac. If there is no spontaneous flow of fluid, the pregnant woman can be asked to perform the Valsalva maneuver or the doctor himself can compress the uterine fundus, in search of induced flow.[9]

If the diagnostic doubt remains, an additional test can be used, such as: a) Phenol Test; b) pH reagent strips; c) "Fern Test" or Crystallization Test in heated blade. These are the classic tests, available in the national reality. However, more recently, other tests have become available, with approval by ANVISA in 2013. These are the immunochromatographic tests (IGFBP-1 and PAMG-1), which detect specific proteins in the amniotic compartment, with greater accuracy. As they are still expensive for the Brazilian reality, they are reserved for more difficult cases, such as, for example, in the presence of blood in the cul-de-sac, a situation in which the pH changes independently from the presence of amniotic fluid.[10-12]

Ultrasonography to assess the Amniotic Fluid Index (AFI) may help in the diagnosis of PROM when there is evidence of oligoamnios or decreased amniotic fluid. But for this, a previous assessment of the amount of amniotic fluid is necessary, as a normal AFI does not rule out the picture, as well as oligoamnios does not confirm it.[13]

Current evidence suggests that in women with PPROM between 24 and 34 weeks, the use of antibiotics significantly improved neonatal performance, including prolonging pregnancy, reducing the need for surfactant and oxygen therapy, reducing neonatal infection, and lower risk of brain changes on ultrasound .[1] The use of these antibiotics has not shown long-term deleterious effects for the newborn.[14]

A review of 22 randomized studies with more than 6,000 pregnant women in 2003 and updated in 2010 evaluated the benefits of different types of antibiotics in pregnant women with PROM. The review concluded that antibiotics are effective in prolonging pregnancy from 48 hours to 7 days and reduce the incidence of maternal and neonatal infection.[15]

On the other hand, a randomized controlled study from 1997 argues that although this approach increases the latency period, reducing some neonatal complications, there may be an increase in the rate of necrotizing enterocolitis with certain antibiotics, in addition to no change in perinatal mortality and predisposition to selection of resistant bacterial flora.[16]

Regarding the use of corticosteroids, it is known that a course of betamethasone (12 mg IM in two doses, 24 hours apart) or dexamethasone (6 mg IM in four doses, 12 hours apart) between 24 and 34 weeks should be performed in all pregnant women at risk of premature birth. Both steroids can be used and not one study has been able to show the superiority of one steroid over the other. The administration of a repeat or rescue course of corticosteroids in pregnant women with premature rupture of membranes is controversial and there is insufficient evidence to make a recommendation for or against.[17]

Due to the lack of scientific evidence on the benefits of using prophylactic tocolysis in the presence of preterm labor, this should not be indicated.[1] There is an underlying risk of an unsuspected infectious condition, with contractions often being the first manifestation of a histological chorioamnionitis.[18]

In cases of PPROM, expectant behavior is adopted, which includes periodic assessment of signs of infection and fetal vitality, in order to detect chorioamnionitis and fetal distress. Group B Streptococcus, Chlamydiatrachomatis and Gonococcus cultures are part of this evaluation, as well as a bacterioscopy (GRAM) of vaginal secretion, blood count with leukocyte count and C-Reactive Protein (CRP). On physical examination, signs such as fever, maternal or fetal tachycardia, purulent leukorrhea associated or not with a foul odor, should raise the suspicion of chorioamnionitis.[9] For the assessment of fetal vitality, the fetal biophysical profile is the recommended exam, which is also useful in detecting of chorioamnionitis, through the absence of fetal respiratory movements.[19]

There is no evidence to support the best place to perform expectant management (hospital vs. outpatient). A 2014 systematic review that included 2 small studies, one by Carlane and one by Ryan, showed similar results in perinatal mortality and frequency of chorioamnionitis. However, these should be interpreted very carefully. Therefore, the publication did not recommend one setting or another in clinical practice, due to the lack of evidence of safety.[20,21] However, in a 2018 retrospective cohort study, of 187 women with a single pregnancy and ruptured ovular membranes, 12 had complications (6.4%). Three criteria were observed to significantly increase the risk of a serious complication: rupture of membranes before 26 weeks, non-cephalic fetal presentation, and oligoamnios. The study concludes by saying that the combination of these three criteria is an indication of conventional hospitalization to limit maternal and fetal morbidity. When two criteria are combined, home care must be discussed on a

case-by-case basis. Finally, if only one unfavorable criterion is present, outpatient treatment is adequate.[22]

There is still no consensus regarding the optimal management of PPROM in late preterm infants. Another systematic review concluded that there was little evidence on the benefits and harms of early birth compared to expectant management.[14]

The management of PROM is dependent on the gestational age at which it occurs. Large societies in the obstetric world consider expectant management in PPROM between 33+6 and 37 weeks reasonable, as long as there is no maternal or fetal contraindication. This approach is based on recent studies that did not show advantages in immediate interruption. This is very clear in the study by Algert et al (2016) which shows little significant difference in neonatal sepsis between immediate delivery and expectant management (2% vs. 3%) and neonatal morbidity and mortality for the respective groups (8% vs. 7%) . However, the immediate delivery group needed more mechanical ventilation and spent more time in intensive care when compared to the expectant management group. As for the mothers, the expectant group had a lower rate of cesarean (16% vs. 19%), however, slightly higher rates of antepartum or intrapartum hemorrhage (5% vs. 6%), intrapartum fever (2% vs. 1%), postpartum antibiotic use (4% vs. 3%) and hospitalization.

Therefore, knowing the clinical impacts of expectant management on late preterm infants is of paramount importance, in addition to allowing the estimation of the potential benefit of maternal-fetal outcomes, since such behavior is not routinely used in other state institutions.

Variable	Number of cases (n = 94)	
	F	%
Preterm PROM gestational age		
34w – 34w and 6 d	37	39.4
35w – 35w and 6 d	33	35.1
36w – 36w and 6 d	24	25.5
Gestational age at birth		
34w – 34w and 6 d	15	16.0
35w – 35w and 6 d	37	39.3
36w – 36w and 6 d	42	44.7
Interval in days between PROM and birth		
≤ 2 days	41	43.6
>2 days	53	56.4
Route of delivery		
Caesarean	44	46.8
Normal	50	53.2
Chorioamnionitis		
Yes	4	4.3
No	90	95.7
Puerperal Infection		
Yes	1	1.1
No	93	98.9
Apgar< 7 in the 5th minute		
Yes	3	3.2
No	91	96.8
NB admission to the ICU		
Yes	11	11.7
No	83	88.3
Neonatal death		
Yes	-	0.0
No	94	100.0

NB: Newborn; Preterm PROM: Preterm premature rupture of membranes

ICU: Intensive Care Unit

Table 1 – Distribution of patients regarding variables

Variable	Number of cases (n = 94)	
	F	%
Interval in days between PROM and birth		
1	18	19.1
2	23	24.5
3	13	13.8
4	11	11.7
5	6	6.4
6	5	5.3
7	5	5.3
8	1	1.1
9	2	2.1
10	1	1.1
11	4	4.2
12	0	0.0
13	1	1.1
14	1	1.1
15	2	2.1
16	0	0.0
17	0	0.0
18	0	0.0
19	0	0.0
20	1	1.1

Preterm PROM: Preterm premature rupture of membranes

Table 2 - Distribution of patients regarding the interval in days between PROM and birth

Gestational age of Preterm PROM	NB admission in the ICU				P
	Yes		No		
	f	%	f	%	
34w – 34w and 6 d	4	36.4	33	39.8	
35w – 35w and 6 d	3	27.2	30	36.1	-
36w – 36w and 6 d	4	36.4	20	24.1	
Total	**11**	**100.0**	**83**	**100.0**	

Insufficient sample for testing; w: weeks; d: days

NB: Newborn; Preterm PROM: Preterm premature rupture of membranes

ICU: Intensive Care Unit

Table 3 - Distribution of patients according to gestational age of Preterm PROM and newborn admission to the ICU

Gestational age of the Preterm PROM	Chorioamnionitis				P
	Yes		No		
	F	%	f	%	
34w – 34w and 6 d	2	50.0	35	38.9	
35w – 35w and 6 d	-	0.0	33	36.7	-
36w – 36w and 6 d	2	50.0	22	24.4	
Total	**4**	**100.0**	**90**	**100.0**	

Insufficient sample for testing; w: weeks; d: days

Preterm PROM: Preterm premature rupture of membranes

Table 4 – Distribution of patients according to gestational age of Preterm PROM and chorioamnionitis

Gestational age of the Preterm PROM	Apgar< 7 in the 5th minute				P
	Yes		No		
	F	%	f	%	
34w – 34w and 6 d	-	0.0	37	40.7	
35w – 35w and 6 d	1	33.3	32	35.2	-
36w – 36w and 6 d	2	66.7	22	24.2	
Total	**3**	**100.0**	**91**	**100.0**	

Insufficient sample for testing; w: weeks; d: days

Preterm PROM: Preterm premature rupture of membranes

Table 5 - Distribution of patients according to gestational age of Preterm PROM and Apgar < 7 in the 5th minute

Interval until birth	Chorioamnionitis				p
	Yes		No		
	f	%	f	%	
≤ 2 days	2	50.0	39	43.3	
> 2 days	2	50.0	51	56.7	0.371
Total	**4**	**100.0**	**90**	**100.0**	

Test used: Fisher

Table 6 - Distribution of patients according to the interval until birth and chorioamnionitis

Interval until birth	Apgar< 7 in the 5th minute				p
	Yes		No		
	f	%	f	%	
≤ 2 days	2	66.7	39	42.9	
> 2 days	1	33.3	52	57.1	0.324
Total	**3**	**100.0**	**91**	**100.0**	

Test used: Fisher

Table 7 - Distribution of patients according to the interval until birth and Apgar < 7 in the 5th minute

Interval until birth	Admission of the NB in the ICU				p
	Yes		No		
	f	%	F	%	
≤ 2 days	4	36.4	37	44.6	
> 2 days	7	63.6	46	55.4	0.226
Total	**11**	**100.0**	**83**	**100.0**	

Test used: Fisher

NB: Newborn; ICU: Intensive Care Unit

Table 8 - Distribution of patients regarding the interval until birth and admission of the NB to the ICU

	Admission of the NB in the ICU				
Chorioamnionitis	Yes		No		P
	f	%	F	%	
Yes	-	0.0	4	4.9	
No	11	100.0	78	95.1	0.599
Total	**11**	**100.0**	**82**	**100.0**	

Test used: Fisher

NB: Newborn; ICU: Intensive Care Unit

Table 9 – Distribution of patients regarding chorioamnionitis and newborn admission to the ICU

METHODS

This is a descriptive retrospective observational study, conducted at Hospital Estadual Materno-Infantil Dr. Jurandir do Nascimento, located in Goiânia - Goiás. The project was submitted for approval by the Medical Research Ethics Committee (CEP) of Hospital Estadual Materno-Infantil Dr. Jurandir do Nascimento, following all the ethical precepts that govern research on human beings, in accordance with resolution nº. 466/2012.

Regarding the free and informed consent form (TCLE), the CEP was asked to waive it because it is a retrospective analysis of physical records filed at the SAME of Hospital Estadual Materno-Infantil Dr. Jurandir do Nascimento, without risk of exposure of patients .

The study population consisted of women and newborns who were conducted expectantly in the face of a diagnosis of PPROM with GA > 34 weeks and < 36 weeks and 6 days, admitted to the HMI between January 2019 and January 2020.

This study included women with a single pregnancy, with confirmed PPROM between 34 ± 0 and 36 + 6 weeks of gestation and who were not in labor within 24 hours after rupture of the membranes.

The following were excluded: patients who evolved spontaneously with labor within 24 hours of PPROM; women with multiple pregnancies; women who presented on admission with abnormal cardiotocography (not reassuring), meconium amniotic fluid, signs of intrauterine infection, severe fetal abnormalities, HELLP syndrome (hemolysis, elevated liver enzymes, and thrombocytopenia) or severe preeclampsia; since these situations could indicate termination of pregnancy for reasons unrelated to PPROM.

Data was typed and manipulated in Excel, for further processing of the data using the Statistical Package for Social Science (SPSS) in Windows (version 21.0). Categorical variables will be presented as absolute frequency (f) and percentage value (%).

For comparisons between variables, the chi-square and Fisher tests were used for smaller samples and with a 2x2 matrix. For all tests, a 95% confidence level was considered, that is, $p < 0.05$ was considered significant.

RESULTS

Through the birth registry of the surgical center of the Hospital Materno Infantil de Goiânia, from January 2019 to January 2020, patients whose births occurred between 34 weeks and 37 weeks of gestation were selected. These patients had their medical records analyzed and 94 of them met the inclusion criteria, as well as no exclusion criteria.

Table 1 shows the distribution of patients regarding the analyzed variables. Of the 94 patients, 39.4% (37/94) were between and 34 weeks and 34 weeks and 6 days of gestation, 35.1% (33/94) were between 35 weeks and 35 weeks and 6 days, and 25 .5% (24/94) between 36 weeks and 36 weeks and 6 days. Regarding the gestational age at birth, 16.0% (15/94) were between and 34 weeks and 34 weeks and 6 days of gestation, 39.3% (37/94) were between 35 weeks and 35 weeks and 6 days, and 44.7% (42/94) between 36 weeks and 36 weeks and 6 days.

Regarding the interval of days between PROM and birth, shown in table 2, 43.6% (41/94) occurred within 2 days and 56.4% (53/94) occurred between 3 and 20 days. Furthermore, regarding the mode of delivery, the percentages of cesarean (44/94) and vaginal delivery (50/94) (46.8% vs. 53.2%, respectively) were similar.

Among the 94 patients participating in the study, the percentage of chorioamnionitis was 4.3% (4/94), puerperal infection 1.1% (1/94), Apgar < 7 at the 5th minute 3.2% (3 /94), 11.7% of admission to the ICU (11/94) and 0% neonatal death (0/94).

The gestational age of PPROM and the interval of days until birth were compared. It was observed that there is no significant difference between the gestational age of the PROM and the interval until birth (p=0.240).

When analyzing the distribution of patients in terms of gestational age of PPROM and admission of the NB to the ICU, Chorioamnionitis and Apgar of the NB < 7 in the 5th minute, there was not enough sample for the test (Tables 3, 4 and 5).

The interval of days until birth was compared with the occurrence of chorioamnionitis, Apgar < 7 in the 5th minute and admission of the NB to the ICU. In none of these comparisons there was a significant difference (p=0.371, p=0.324 and p=0.226, respectively).

The occurrence of chorioamnionitis and the NB admission to the ICU were also compared. It was observed that there is no significant difference between chorioamnionitis and admission of the NB to the ICU (p=0.599).

DISCUSSION

In the present study, a low prevalence of chorioamnionitis (4.3%) was observed. Furthermore, there was no statis-

tical significance of the time interval between PPROM and birth and chorioamnionitis (p=0.371). However, according to a meta-analysis published in 2018, which included 3 randomized clinical trials, there was a higher prevalence of chorioamnionitis in expectant management compared to immediate delivery (6.4% x 1.3%), with statistical significance (p < 0.0001).[24,25,26]

At the Hospital Materno Infantil de Goiás, prophylactic antibiotics are routinely administered to all pregnant women who have PPROM, in order to increase the latency period between the rupture of the bag and birth. Although it was not the objective of this study to evaluate the effects of prophylactic antibiotics, a low rate of puerperal infection was evidenced (only one case, corresponding to 1.1% of the sample). Similarly, a meta-analysis containing five clinical trials with 2,699 patients described that patients who received prophylactic antibiotic had the same risk of chorioamnionitis (2.7% versus 3.7%; relative risk [RR]: 0.73), endometritis (0.4% versus 0.9%; RR: 0.44), maternal infection (3.1% versus 4.6% RR: 0.48) and neonatal sepsis (1.0% versus 1.4%; RR: 0.69).[28]

Studies that analyzed the rate of admission to the maternal ICU for complications of PPROM were not found in the literature. However, there is data in the literature regarding severe maternal outcomes. In a retrospective cohort study with 118 participants, 78 underwent active management (group I) and 40 underwent expectant management (group II). In both groups there were no cases of sepsis and/or maternal death, which indirectly meets the results found in the present study, which did not present any case of admission to a maternal ICU, where, in general, critically ill and/or life-threatening patients are referred. [27]

As mentioned above, it was not possible to use tests to assess whether there was statistical significance in the comparison between the gestational age of PPROM and Apgar < 7 in the 5th minute.

Regarding the comparison between the time interval until birth and Apgar < 7 in the 5th minute, it was possible to use the test and it did not show any statistical difference. In agreement with the aforementioned meta-analysis, with 2572 cases of PPROM, which also did not present a statistically significant difference between the groups undergoing immediate delivery or expectant management.[24-27]

The admission rate of NBs to the ICU in the studied sample was 11.7% (11/94). In the above-mentioned meta-analysis, there were higher rates of this outcome and with a statistically significant difference between the groups, and in the immediate delivery group there was a higher rate (69%) and expectant management (59%), p value < .0001.[24-27]

When comparing the gestational age of PPROM and the newborn's admission to the ICU, the sample was not sufficient for statistical testing. Regarding the interval of days between PPROM and birth versus admission of the NB to the ICU, there was no statistically significant difference.[24,25,26]

Finally, neonatal death was not observed in our sample. In the aforementioned meta-analysis, published in 2018, one neonatal death was observed in the group undergoing expectant management (1/1281) and two deaths in the group undergoing immediate delivery (2/1291). Therefore, due to the low prevalence of this outcome, it was not possible to apply tests to assess the statistical significance.[24,25,26]

CONCLUSION

In women with late PPROM, expectant management, as well as immediate delivery, are acceptable alternatives, given the balance, so far known in the literature, of advantages and disadvantages for the maternal-fetal binomial.

In addition, we suggest extending the study time and, consequently, the sample, so that the expectant approach, which is still little used in other services in Brazil, continues to be adopted at Hospital Estadual Materno Infantil Dr. Jurandir no Nascimento, once that it will be possible to apply statistical tests on all analyzed outcomes and/or find statistical differences that justify a change in conduct.

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