

## EXPECTANT VERSUS ACTIVE MANAGEMENT WITH OXYTOCIN FOR PREMATURE RUPTURE OF MEMBRANES AT TERM

### *CONDUTA EXPECTANTE VERSUS ATIVA COM OCITOCINA NA ROTURA PREMATURA DE MEMBRANAS A TERMO*

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#### ABSTRACT

##### **Objective**

To compare the expectant and the active management with oxytocin for premature rupture of membranes at term.

##### **Method**

A multicentric randomized clinical trial was carried out, evaluating variables concerning labor and delivery complications, and other maternal and neonatal outcomes. Two hundred pregnant women with premature rupture of membranes at term were selected from four public hospitals in the State of São Paulo, Brazil. They were randomly divided into two groups: active management, with oxytocin induction if labor had not initiated spontaneously within the first six hours after the rupture; and expectant management, waiting for the spontaneous onset of labor up to 24 hours. For the statistical analysis the Chi-square, Mann-Whitney, Fisher's Exact, Student's t tests were used.

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## Results

The values for the main variables were not significantly different between the groups, although the negative outcomes were concentrated in the expectant management group. Only the latent period and the time between the rupture of the membranes and the delivery were significantly longer for the expectant management than for the active management with oxytocin stimulation.

## Conclusion

Although the results did not show very important differences between the two managements for premature rupture of membranes at term, the active management had a relatively better performance.

**Index terms:** PROM, labor induced, pregnancy, high-risk, oxytocin, fetal membranes, premature rupture.

## RESUMO

### Objetivo

Comparar a conduta expectante *versus* ativa com ocitocina na rotura prematura de membranas ovulares a termo.

### Método

*Realizou-se um ensaio clínico multicêntrico, controlado e aleatorizado, avaliando complicações maternas e perinatais associadas ao trabalho de parto e ao parto em gestantes com diagnóstico de rotura prematura de membranas no termo. Foram selecionadas 200 gestantes com esse diagnóstico, atendidas em quatro instituições públicas do Estado de São Paulo, Brasil. Elas foram aleatoriamente divididas em dois grupos de conduta: ativa com ocitocina se o trabalho de parto não tivesse se iniciado espontaneamente dentro das primeiras seis horas após a rotura; e expectante, aguardando-se o início espontâneo do trabalho de parto por um período máximo de 24 horas. Para a análise estatística foram utilizados os testes de qui-quadrado, Mann-Whitney, Exato de Fisher e t de Student.*

### Resultados

*Os valores das principais variáveis estudadas não foram significativamente diferentes entre os dois grupos, embora os resultados negativos tenham se concentrado no grupo de conduta expectante. Somente o período de latência e o tempo entre a rotura de membranas e o parto foram significativamente maiores no grupo de conduta expectante, em comparação com o grupo da conduta ativa através de indução com ocitocina.*

### Conclusão

*Apesar de os resultados não terem mostrado diferenças muito importantes entre os dois grupos de conduta para gestações com rotura prematura de membranas a termo, a conduta ativa teve um relativo melhor desempenho.*

**Termos de Indexação:** RPM, trabalho de parto induzido, gravidez de alto risco, ocitocina, ruptura prematura de membranas fetais.

## INTRODUCTION

Premature rupture of membranes (PROM) is observed in approximately 10% of all pregnancies<sup>1</sup>, representing one of the most frequent complications. Among the factors possibly related to PROM, inflammatory alterations associated with infections have been receiving stronger support<sup>2</sup>. However, infectious etiology of PROM remains still controversial, specially taking into account the results which came up from a recent megatrial where the use of broad-spectrum antibiotics for preterm prelabor rupture of membranes did not show a clear maternal and perinatal benefit<sup>3</sup>.

Several problems can occur due to PROM, not only maternal but also perinatal. The main maternal risk is infection, which can appear in different ways, from the puerperal endometritis to septicemia secondary to chorioamnionitis. Prematurity, perinatal infection and complications associated with the generally resultant oligohydramnios are important consequences for fetuses and newborns. All of them, in addition to the increase in instrumental and cesarean deliveries, could theoretically be attributed to a conservative management for PROM<sup>4</sup>.

The most important risks run by pregnant women with premature rupture of membranes at term (PROM-T) are amniotic infections and complications derived from oligohydramnios. Labor starts spontaneously within the first 24 hours after the rupture in about 80% of the cases<sup>5</sup>. Furthermore, the risk of chorioamnionitis increases if the latent period goes beyond 24 hours, but it does not increase significantly before that interval<sup>4,6,7</sup>.

The active management, with the immediate use of oxytocin to induce labor, has been considered the safest alternative to avoid the maternal and perinatal risks of infection<sup>8</sup>. However, during the last decade, several authors have found that the immediate induction of labor

with oxytocin leads to a significant increase in the incidence of Cesarean sections<sup>7,9,10,11</sup>. Besides, these high Cesarean section rates seem to be associated with failure of labor induction, particularly if the cervix presents unfavorable conditions and ripening agents are not available. According to these authors, an expectant management, waiting for the spontaneous onset of labor for a mean period of 24 to 48 hours, could help to decrease this high incidence of Cesarean sections.

Considering that approximately 80% of the pregnant women with PROM-T will probably start labor spontaneously within a maximum period of 24 hours, and that the risk of infection within this period does not rise significantly, just 20% of the cases would really need an induction of labor. Obviously, if the high Cesarean section rates are in fact related to the active management with oxytocin, a decrease in these rates would be presumed with the expectant management.

The purpose of this study was to compare two possibilities of obstetrical management in low-income pregnant women with PROM-T in Brazil – active with oxytocin and expectant for 24 hours before labor induction, evaluating the variables related to labor, maternal and neonatal complications.

## SUBJECTS AND METHODS

This was a multicentric, prospective, controlled and randomized clinical trial. Based on two similar previous trials<sup>9,10</sup>, applying the procedures recommended by Pocock<sup>12</sup> and taking as reference the percentage of Cesarean sections, the size of the sample was estimated in 98 for each group. Admitting an  $\alpha$  error of 5% and a power ( $1-\beta$ ) of 80%, 200 pregnant women with the diagnosis of PROM-T were selected and randomly allocated to one of the groups, expectant management (96) or immediate labor induction with oxytocin (104). This trial was performed in four public institutions in the State

of São Paulo, Brazil, which provide medical assistance to the low-income population. The study protocol was previously evaluated and approved by the Institutional Review Board of these four institutions.

The following inclusion criteria were adopted: PROM in the last six hours or less, pregnancy at term ( $\geq 37$  completed weeks), with only one live fetus, in cephalic presentation, clear amniotic fluid, absence of maternal or fetal factors that could require the immediate interruption of pregnancy and voluntary agreement to participate in the trial. The exclusion criteria were: pregnant women already in labor, with two or more previous Cesarean sections or a non segmental uterine scar, any contraindication to vaginal birth, diabetes, cardiopathies, genital hemorrhage, severe anemia or any other pathological condition which would disable the woman to participate in the trial.

Route of delivery, neonatal infection, maternal infection, Apgar score, latent period, interval between PROM and delivery, and the weight of the newborn in each group were compared. Maternal age, gestational age, school level, parity, ethnic group, history of Cesarean sections, cervix condition, and the interval between PROM and the hospital admission were also evaluated and compared.

After the diagnosis of rupture of the membranes was confirmed by clinical and laboratory data (crystallization test, vaginal pH determination or ultrasound exam) and the time of the rupture was informed by the patient, the groups of pregnant women had the following standard follow-up below:

**Active Management:** An intravenous oxytocin infusion was initiated immediately after admission, increasing the perfusion rate every 30 minutes until an effective uterine contractions pattern was reached. Electronic fetal monitoring was performed at admission and then repeated

intermittently throughout the period of labor induction.

**Expectant management:** The pregnant woman was admitted, an intermittent electronic fetal monitoring was performed, her pulse and temperature and the fetal heart rate were controlled for a period of 24 hours or until the onset of spontaneous labor. In case the labor did not start spontaneously in a maximum period of 24 hours, the same procedures as for the active management were adopted. Acceleration of labor with the administration of oxytocin was carried out according to clinical judgement, if labor did not progress due to deficient uterine contractility.

For numeric variables, the means and the standard deviations were calculated in each group, the Student's "t" test was used for continuous variables and the Mann-Whitney test for discrete variables or those with a non-normal distribution. For qualitative variables, the  $\chi^2$  or the Fisher's Exact tests were used. Some other results of this trial had already been published<sup>13</sup>.

## RESULTS

The results concerning the distribution of the control variables confirm that the groups were homogeneous (Table 1). The weights of the newborns were not significantly different between both groups. In the expectant management group, approximately a third of the women (34%<sup>9</sup> started labor spontaneously in the first six hours, 71% in the first 12 hours and 85% within the first 24 hours. The remaining 15%, who did not start labor spontaneously within 24 hours, had their labor induced with oxytocin. Almost half of them (6/13) did not respond to the induction satisfactorily, and they had to undergo a Cesarean section.

Approximately two thirds of the deliveries were vaginal, in a similar way in both groups. However, the number of Cesarean sections

performed due to induction failure was significantly higher in the group with active management and those due to other causes were twice higher in the expectant one (Table 2). The other causes of Cesarean sections in the expectant management group included four occurrences of acute fetal distress and nine of dystocia. In the active management group, there were three occurrences of acute fetal distress and six of dystocia.

The great majority of the newborns had Apgar scores for the first and fifth minutes equal to or higher than seven, in a similar way in both groups of management (Table 3). In the group of expectant management, three newborns had Apgar scores for the fifth minute lower than seven. One presented Respiratory Distress Syndrome, one had septicemia and the third had

hypoxia associated with septicemia. The mean number of days of hospitalization for the newborns was also not significantly different between the groups.

Five cases of neonatal infection were diagnosed in the expectant group and two in the active one (Table 3). Among the cases of neonatal infection in the active management group, one mother had vaginal delivery and the other underwent Cesarean section. Among the cases in the expectant management group, one had vaginal childbirth and four underwent Cesarean sections.

In the active management group there were four positive hemocultures from blood of the umbilical cord (one for *Staphylococcus aureus*, one for Group B *Streptococcus* and two for *Staphylococcus epidermidis*), without any

**Table 1.** Value of some control variables of pregnant women with PROM-T by management.

Variables	Management				p
	Active		Expectant		
	Mean	SD	Mean	SD	
Maternal age (years)	24.37	6.11	24.53	6.61	NS*
Parity	1.11	1.85	1.24	2.14	NS**
Number of pregnancies	2.35	2.02	2.33	2.37	NS**
Gestational age (weeks)	38.95	1.18	38.74	1.41	NS*
Bishop Index	5.94	2.58	5.56	2.42	NS**
Rupture-admission interval (hours)	3.17	1.62	3.42	1.70	NS*

\*Student's "t" test; \*\* Mann Whitney test.

**Table 2.** Distribution of the pregnant women with PROM-T by route of delivery and management.

Route of delivery	Management	
	Active	Expectant
Vaginal birth*	70	72
C-section due to induction failure	25	6
C-section due to other causes	9	18
Total (n)	104	96

$\chi^2=14.38$   $p<0.001$   
 \*vaginal x cesarean  $\chi^2=1.43$   $p= 0.231$

**Table 3.** Distribution of pregnant women with PROM-T according to some maternal and neonatal outcomes and management.

Main outcomes	Management		p*
	Active	Expectant	
Apgar <7 1 <sup>st</sup> min**	13	12	0.839
Apgar <7 5 <sup>th</sup> min	0	3	0.108
Neonatal infection	2	5	0.264
Neonatal death	0	1	0.480
Maternal infection	1	2	0.608
Total (n)	104	96	

\* Fisher's Test; \*\*Chi-square Test.

clinical sign of local or widespread infection and without other laboratory alterations. The women delivered vaginally and were just observed. No antibiotics were applied and all of them had good evolution. A neonatal death occurred in the expectant management group due to hypoxia associated with septicemia.

Maternal infection was low in both groups. There were only two cases of infection in the expectant and one case in the active group. These three mothers had wound infection after the Cesarean sections, with no uterine or systemic involvement. They also had good evolution, after appropriate antibiotic was used.

The latent period and the interval from rupture of membranes to delivery were significantly shorter in the active than in the expectant group. It was also observed that the onset of labor and the delivery occurred significantly earlier in the active management group (Table 4). This was also valid when the maximum intervals of 12 or 24 hours were considered.

## DISCUSSION

The results of this trial indicate that there seems to be no significant differences in the

Cesarean section rates and in the proportion of maternal and neonatal complications, when adopting the expectant or active management with oxytocin for pregnant women with PROM-T. In both groups, the values of the main dependent variables such as the incidence of Cesarean section, maternal and neonatal rates of infections and Apgar scores were very similar. The most evident difference was the shorter duration of the latent period and of the interval between PROM and labor in the active management.

The available literature on this subject shows great disagreement among the results obtained by authors of several countries. Many of them showed a decrease in the incidence of Cesarean section, mainly due to induction failure, in case of expectant management, instead of the immediate induction of labor with oxytocin<sup>10,11</sup>. The absence of any difference in this rate observed in the present study coincides with several other authors<sup>6,14-16</sup>. However, when the incidence of Cesarean section exclusively due to failure of labor induction was analyzed, a considerably higher value was found in the active management group, which is also in agreement with most of the revised trials. A factor that may have affected these results is the existent differences in medical behavior all over the

**Table 4.** Distribution of pregnant women with PROM-T according to latent period and PROM to delivery intervals, by management.

Interval (hours)	Latent period		PROM to delivery	
	Active	Expectant	Active	Expectant
≤ 6	48	33	1	1
>6 – 12	51	35	36	20
>12 – 18	5	12	13	18
>18 – 24	0	3	23	26
>24	0	12	0	20
<i>p</i> *	<0.0001		<0.0001	
<b>Total (n)</b>	104	96	104	96

\*Chi-square for trend test.



country. The liberality with which Cesarean sections are performed may have contributed to the increase in its incidence, especially in the expectant management group.

Another factor that can be associated with the lack of difference in the rates of Cesarean sections between the groups is a possible selection bias in the sample of subjects. Women were admitted within six hours of PROM, provided they were not in labor at the moment of hospitalization. The ones who started labor spontaneously before admission were excluded from the study. That might have affected the results, perhaps decreasing the number of pregnant women with higher probability of presenting favorable responses in the expectant management group.

The rates of Cesarean sections were relatively high in both groups (33% and 25% respectively for the active and the expectant management). In spite of the statistical insignificance of the difference found between the groups, the rate of Cesarean sections was, in fact, lower in the expectant management one. It is even possible to infer that, maintaining the same difference and observing a larger number of cases, such difference could have been significant.

Another major concern about the treatment of pregnant women with PROM is the great risk of infection to which, in general, they are exposed. The incidence of maternal infection in this trial - 2.1% in the expectant and 0.9% in the active management group - was low, considering what would be expected as an overall rate in the four participant centers, and they were restricted to the incisions of Cesarean sections. The incidence of neonatal infection, five cases (5.2%) in the expectant and two (1.9%) in the active management group, was higher than the global means of neonatal infection in the centers involved in the present study. However, they are similar to the values found by other authors in trials like this<sup>6,8,17</sup>.

The maternal and neonatal cases of infection affecting pregnant women at term present, in general, good response to the appropriate treatment with antibiotic<sup>18</sup>. In fact, the maternal and neonatal cases of infection in this trial, appropriately treated with wide-spectrum antibiotics, presented good evolution, without any sequel probably related to the infection.

One case of the expectant management group constituted an exception, for the newborn died, after 57 days of hospitalization in an Intensive Care Unit. The cause of death was not associated exclusively with the infection, but also with serious hypoxia during expulsive period and massive aspiration of meconium.

It would be reasonable to conclude therefore that the expectant management would be related to an increase in the maternal and neonatal risk of infections, considering the longer duration of the latent period in this kind of management. However, this would be true only for periods of rupture of membranes longer than 24 hours, and only one out of the seven cases of infection in this trial presented such a characteristic.

Another important factor that may be associated with increase in the maternal and perinatal incidences of infection is the vaginal exam during latent period, as well as its repetition during this period<sup>18</sup>. There is a probability of the expectant management being more appropriate in the cases of immature uterine cervix. In those with a Bishop index equal to or higher than five, labor induction seems to be the most adequate therapeutic option. In this trial, the vaginal cervix examination was performed only after the onset of labor. Another option would be the systematized cervical examination in the cases of PROM-T, through a speculum exam, as proposed by some authors<sup>19</sup>. In the present study, however, such procedure was not used.

It should be highlighted that the pregnant women with PROM-T who participated in this

trial did not present a higher infection risk, when compared to the ones from developed countries. There are clear differences between these two kinds of individuals, mainly concerning nutrition and health aspects. The pregnant women in the current study came from populations with serious social problems and, therefore, an increase in the risk of infection could be reasonably expected. However, that did not happen.

The conditions of children at birth were also evaluated. For such analysis, the Apgar scores of the first and fifth minutes of life were used. The present results are similar to the ones of the great majority of authors, who did not observe any significant differences in these scores between these two managements<sup>6,14</sup>.

## CONCLUSION

The available literature was reviewed as far as possible, and this seems to be the first Brazilian randomized clinical trial comparing two therapeutic possibilities for dealing with pregnant women with PROM-T. The results are in accordance with those from the literature, although some practical constraints should be taken into account. For instance, one would be the absence of maternal and neonatal regular assistance after the discharge from the hospital. Then, some cases of infection might have occurred after that, but not identified.

It is also important to accept that, although no clear advantages were found in inducing the labor of pregnant women presenting PROM-T with the use of oxytocin, the expectant management is not necessarily the best form of therapeutic approach for these patients. In the present trial, the comparison was only between the expectant management and the induction of the labor with oxytocin. Maybe such substance is not the best option for labor induction anymore.

Other possible safe alternative for labor induction in pregnant women with PROM-T,

mainly in those with unfavorable cervix, is the use of prostaglandin E<sub>2</sub> or E<sub>1</sub> methyl-analogue<sup>20,21</sup>. In Brazil, up to now, the only prostaglandin available exclusively for hospital use is the E<sub>1</sub> methyl-analogue (misoprostol), which seems to present advantages over the natural prostaglandins<sup>21</sup> and also over oxytocin.

PROM-T is an obstetrical occurrence of extreme importance. It contributes to the worsening of the maternal and neonatal health indexes, and may cause, among other adversities, a significant increase in the incidence of Cesarean sections. Therefore, it is necessary to carry out new trials, with larger samples and with extended maternal and neonatal follow ups.

It is expected that somehow the results obtained in this trial contribute to a better understanding of this important obstetrical situation, providing conditions to determine the best therapeutic approach for these pregnant women.

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