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Preterm premature rupture of membranes: management between 28 and 34 weeks of pregnancy

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ABSTRACT

Introduction: Premature rupture of membranes remains a challenge for professionals due to the high rates of maternal and neonatal morbidity and mortality, mainly related to complications resulting from prematurity. **Objective:** To analyze the scientific production about premature rupture of membranes in pregnancies above 28 weeks and below 34 weeks. **Methods:** Integrative literature review carried out in the Lilacs, SciELO, Medline and Cochrane Library databases, between 2014 and 2018, in Portuguese, English and Spanish, including original articles, available in full online, with free access, that addressed the study theme, using the keywords "premature rupture of ovular membranes", "premature labor" and "pregnancy complications" combined using the Boolean operators "AND" and "OR". **Results:** Fourteen studies were included. It was possible to highlight the main recommendations regarding preterm premature rupture of membranes, divided into six categories for discussion, namely: indications for expectant management and delivery induction, prophylactic antibiotic therapy, prenatal corticosteroids, use of tocolytics, recommendations regarding the use of magnesium sulfate and amniocentesis. **Conclusion:** It was identified that expectant management is the ideal approach, with constant monitoring of the pregnant woman and the fetus, in addition to the administration of prophylactic antibiotics and prenatal corticosteroids, in the face of premature rupture of membranes in pregnancies between 28 and 34 weeks in order to provide the best maternal and perinatal results, guiding health professionals to evidence-based practice.

Keywords: fetal membranes, premature rupture; obstetric labor, premature; therapeutics.

INTRODUCTION

The premature rupture of membranes (PROM) is the spontaneous separation of the chorionic and amniotic membranes before the onset of labor, regardless of gestational age[1]. The American College of Obstetricians and Gynecologists (ACOG) conceptualizes that, when it occurs before 37 weeks of gestation, it is termed preterm premature rupture of membranes (PPROM)[2].

According to the commission specialized in prenatal care from the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo), PPROM has an incidence of 2 to 3% of all pregnancies and is responsible for 32.6% of premature births in the United States of America and 18.2% in Brazil[1]. It continues to be a challenge for obstetricians due to the high rates of maternal and neonatal morbidity and mortality, mainly related to complications resulting from prematurity.

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The main maternal consequence is the risk of chorioamnionitis and postpartum infection, which increases the longer the latency period, the time between rupture of the membranes and delivery[2]. In pregnancies complicated by chorioamnionitis, the chances of preterm delivery increase, as well as its complications, such as the risk of developing sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and the main and most frequent one, respiratory distress syndrome in the newborn, besides being related to delays in neuronal development[2,3-5]. Other possible complications are premature placental abruption, umbilical cord prolapse, and the need for cesarean delivery.

Ascending infections of the genitourinary tract, chronic inflammation, uterine contractions, second and third trimester bleeding, stress and fetal movement, isthmus cervical incompetence, low placenta insertion, uterine distension caused by twin pregnancies or polyhydramnios, low body mass index, smoking, use of illicit drugs and low socioeconomic status are among the main spontaneous causes and known risk factors[2,5,6]. Among the iatrogenic causes are PROM after amniocentesis and chorionic villus sampling, invasive procedures used to correct fetal anomalies before birth, and trauma[5].

Diagnosis is primarily made by the pregnant woman's history, with reports of fluid loss through the vaginal canal, and physical examination. It is recommended for the speculum examination to be performed sterilely and vaginal touches avoided, unless they are extremely necessary, to decrease the risk of intra-amniotic infection[2]. In case of doubt, the diagnosis can be corroborated by vaginal fluid pH testing, ultrasound examination to evaluate the volume of amniotic fluid or the less specific fetal fibronectin test[2,3]. However, the diagnostic accuracy can be improved by immunochromatic tests that aim to detect specific substances of the amniotic fluid in the secretion collected from the vaginal environment (Actim Prom® and AmniSure®). The literature establishes very good sensitivity and specificity values related to these tests[7].

The best approach to pregnant women with PPROM is still not well established, differing among obstetricians and being mainly based on gestational age, which is used to guide the management between expectant management or induction of labor. After an initial evaluation of the pregnant woman and the fetus for factors that indicate immediate induction of labor, such as established intra-amniotic infection, active labor and fetal distress, expectant management is considered[8].

Therefore, this integrative literature review aims to identify the most recent evidence on the management of premature rupture of membranes in pregnancies above 28 and below 34 weeks that provide the best maternal and perinatal outcomes, to guide health professionals to evidence-based practice.

METHODS

The integrative review method was used to gather and systematize data from studies that provide evidence of the best national and international approaches to the premature rupture of membranes in pregnancies above 28 and below 34 weeks.

This review was guided by the following question: "What conduct should be taken when facing the premature rupture of ovular membranes in pregnancies above 28 weeks and below 34 weeks?", prepared through the PICO strategy[9] (P - Patient or problem: pregnant women with premature rupture of ovular membranes; I - Intervention or indicator: conservative management or induction of labor; C - Control: pregnant women from 28 to 34 weeks; O - Expected results: management that provides better maternal and perinatal outcomes). The chosen inclusion criteria were: publication in the last five years, from 2014 to 2018, in Portuguese, English, and/or Spanish, original articles, available full text online with free access, and that address the theme of the study.

Experience reports, reflection studies, commentaries, abstracts of proceedings, duplicate publications, theses, master theses, books, and articles that did not meet the scope of this review were excluded.

The search for the studies was conducted in May 2019 in the following databases: Latin American and Caribbean Literature in Health Sciences (Lilacs), Scientific Eletronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (Medline) and Cochrane Library.

As a research strategy, the Health Science descriptors DeCS were used for the Portuguese language databases, and the corresponding Medical Subject Headings (MeSH) in English, related to the study theme: "Preterm premature rupture of membranes", "premature labor" and "pregnancy complications". These descriptors, combined with the Boolean operators AND and OR, allowed the following cross-references (C): C1 ("Preterm premature rupture of membranes" AND "premature labor") and C2 ("Preterm premature rupture of membranes" AND "pregnancy complications"), combined in each database until the number and specificity of articles were retrieved.

After cross-referencing, 2,246 articles were identified in the Medline database, 494 in the Cochrane Library, 159 in Lilacs, and 43 in SciELO, totaling 2,942 publications. After applying the inclusion criteria, 384 publications were identified, of which 49 were excluded for duplicity, totaling 335. The next step was carried out by reading the title, abstract, keywords, or descriptors, excluding 310 articles that were not related to the theme, totaling 25 studies for reading in full. Subsequently, the articles were read, aiming to organize the data into thematic categories. Then, the articles were grouped according to their content and suitability to the theme. The final sample was composed of 14 articles. The selected studies were categorized in a Microsoft Excel® file.

RESULTS

The final sample of this review consisted of 14 scientific articles, which met the proposed inclusion criteria. A total of 8 (57.1%) of the included publications were extracted from Medline database, followed by 4 (28.6%) from Cochrane and 2 (14.2%) from SciELO. No articles answering the research question were found in the Lilacs database.

As for the year of publication, they are between the years 2014 and 2018, with 3 (21.4%) dating from 2018, 5 (35.7%) from 2017, 1 (7.1%) from 2016, 4 (28.6%) from 2015, and 1 (7.1%) from 2014. Regarding language, 12 (85.7%) studies were published in English and 2 (14.3%) in Spanish. The research methods were: 5 (35.7%) literature reviews, followed by 4 (28.6%) randomized clinical trials, 3 (21.4%) expert recommendations based on scientific evidence, 1 (7.1%) quantitative study, and 1 (7.1%) retrospective cohort study.

DISCUSSION

To answer the research question of this integrative literature review, the 14 articles included were divided into six thematic categories for discussion, namely: indications for expectant management and induction of labor, prophylactic antibiotic therapy, prenatal use of corticosteroids, use of tocolytics, recommendations regarding the use of magnesium sulfate, and performance of amniocentesis.

Category 1: Indications for expectant management and induction of labor

Two of the included studies found no statistically significant differences when comparing expectant management with induction of labor in pregnancies complicated by PPROM up to 34 weeks gestational age[3,10]. However, in the systematic review and meta-analysis published in 2017, an increased risk of Respiratory Distress Syndrome (RDS), sepsis, neonatal death, and chorioamnionitis associated with induction of labor in pregnancies between 28 and 34 weeks[3] was evidenced. A 2017 Cochrane literature review[11] also found that preterm birth was associated with higher rates of cesarean sections, newborns with lower gestational ages, increased rates of neonatal death and RDS requiring mechanical ventilation, and a higher number of admissions to Neonatal Intensive Care Units.

The other evidence found in the literature[2,4,8] reinforces that in pregnancies complicated by PROM between 28 and 34 weeks of gestational age it is recommended that an initial assessment of the pregnant woman and fetus is performed, in order to guide the conduct between induction of labor or expectant management. The initial evaluation should include appropriate estimation of gestational age at the time of rupture, evaluation of fetal presentation and well-being, investigation of signs and symptoms suggestive of intra- amniotic infection, placental abruption, active labor, and fetal compromise.

It consists of hospital admission of the pregnant woman with periodic evaluation for early identification of signs that indicate immediate termination of pregnancy, periodic ultrasound monitoring of the fetus, in addition to the administration of schemes for induction of fetal lung maturity and antibiotic prophylaxis. Periodic cardiotocography is recommended because it allows the detection of fetal tachycardia and decreased fetal variability, indicative signs of chorioamnionitis[2,4,8].

Such evidence regarding the indications for expectant management and immediate termination of pregnancy agree with the clinical protocol prepared by the national committee specialized in prenatal care of Febrasgo[1], however, they differ with respect of up to what gestational age it is recommended to follow the expectant management. The articles included in this review recommend expectant management up to 34 weeks of pregnancy, based on a risk-benefit ratio, since after 34 weeks the risk of chorioamnionitis and neonatal infection increases, in addition to the fetus having already reached the desired pulmonary maturity[2,4,8,12]. Some studies still recommend inducing labor before 34 weeks in case of proven fetal lung maturity through amniocentesis[4,8].

Regarding induction of labor, some indications found in a recent study are premature rupture of membranes, preeclampsia, intrauterine growth restriction, fetomaternal alloimmunization or intrahepatic cholestasis[13,14].

According to recommendations of the Polish Gynecological Society[12], when considering inducing labor, the pregnant woman should be assessed for gestational age based on the first-trimester ultrasound, the severity of symptoms, parity and maturity of the cervix, and the presence of contraindications.

For assessment of cervical maturity, the articles included in this review recommend the use of Bishop's score[7,12], however they differ on the score that indicates mature cervix. A review of the literature[7] found that a score <8 indicates the need to initiate the process for cervical maturation, while the Polish Gynecological Society[12] agrees with the technical manual for high-risk pregnancy published in 2012[15] by the Brazilian Ministry of Health, which recommends initiating the process for cervical maturation in case of Bishop score below 6.

Among the methods for induction of cervical maturity, the articles included in this review feature osmotic, mechanical, and pharmacological dilators[8,12]. Osmotic dilators are not recommended because of the high rates of peripartum infection[8].

Mechanical methods were comparable to pharmacological methods regarding induction of labor within 24 hours and risk of cesarean section, with a lower risk of uterine hyperstimulation[12]. Mechanical dilators (Foley balloon or double-balloon catheter) in previous studies were associated with risks of ascending infection, with PROM being a relative contraindication for their use, but

induction of labor initiated with a Foley balloon was also shown to have a shorter latency period and lower incidence of chorioamnionitis compared with induction using misoprostol alone[8,12].

The Polish Gynecological Society[12] recommends the use of PGE2 (dinoprostone) or PGE1 (misoprostol) as a pharmacological method, with proven greater efficacy through vaginal administration, in accordance with the recommendations of the Manual for High-Risk Pregnancies of the Brazilian Ministry of Health[15]. It is noteworthy that the studies recognize the lack of effectiveness of the vaginal application of pharmacological methods, when there is loss of fluid and there may be continued expulsion of the drug, thus being indicated other routes of administration, such as the oral route[12,15-17].

Due to the stronger uterotonic effect of misoprostol and the risk of uterine hyperstimulation and impaired fetal well-being, it is recommended, after its administration, the fetus and the pregnant woman be monitored continuously[4,12,16].

Both oxytocin and misoprostol are effective in inducing labor, with similar maternal and fetal outcomes. Oxytocin has a shorter interval to labor time of more than 3h when compared to prostaglandin. Vaginal prostaglandin shows superiority over intravenous oxytocin in its ability to mature the cervix in 5h, as well as to achieve vaginal delivery in 24h[8]. The referred study did not differentiate non-favorable from favorable cervices at the time of induction. This is a bias since misoprostol is more indicated in ripening unfavorable cervicals and the use of oxytocin in favorable cervicals and it is common knowledge that prostaglandin works in ripening the cervix[17].

A large prospective trial of 240 women from Turkey found that higher doses of oxytocin may be needed in cases of nulliparous women with gestational age <36 weeks and cervical dilation <2 cm, with the most serious complication related to its use being the risk of uterine hyperstimulation[12].

Category 2: Prophylactic antibiotic therapy

The evidence present in the literature and included in this review[2,8,12,16] recommends the use of prophylactic antibiotic therapy in the occurrence of PPROM and reports an association with prolonged pregnancy and reduced maternal and neonatal morbidity by reducing the rates of neonatal infection, chorioamnionitis, newborn respiratory distress syndrome, need for oxygen and surfactant, bronchopulmonary dysplasia, necrotizing enterocolitis, and abnormal brain ultrasonographic findings. Such recommendations are not in agreement with the clinical protocol published by Febrasgo[1], in which the administration of prophylactic antibiotics during expectant management in the occurrence of PPROM is not recommended, despite its effect in prolonging pregnancy and reducing neonatal complications, because it refers to an association specifically to the use of amoxicillin with potassium clavulanate, to the incidence of necrotizing enterocolitis, besides leading to increased resistance of bacteria.

Regarding the best antibiotic regimen for prophylaxis, recommendations differ among the available evidence. In an annual report by the Committee on Perinatology and the Japanese Society of Obstetrics and Gynecology[10], it was found that penicillin, together with second-generation cephem agents, and combinations of penicillin with a macrolide were the most frequently used antibiotics in institutions in Japan. The average length of treatment differed, being one week, up to 34 weeks of pregnancy, until signs of infection improved or until delivery[10]. In the Guide for Clinical Practice published in the Colombian Journal of Obstetrics and Gynecology[4], the recommendations are to administer erythromycin orally for 7 days or ampicillin with erythromycin intravenously and orally combined for 7 days. A retrospective cohort study[16] comparing two antibiotic regimens found that the combination of ceftriaxone (1g) intravenously, every 24 hours, clarithromycin (500mg) orally, every 12 hours, and metronidazole (500mg) intravenously, every 8 hours increased the latency period, reduced rates of acute histological chorioamnionitis, funalisitis, intraventricular hemorrhage, cerebral palsy, and rates of spontaneous preterm birth within 7 days. The superiority of this regimen has been demonstrated against mycoplasmas, anaerobic and aerobic microorganisms, in addition to the increased transplacental passage, and has been administered up to the time of delivery[14]. In contrast, the American College of Obstetricians and Gynecologists (ACOG)[2] recommends a 7-day regimen with intravenous administration of ampicillin and erythromycin, followed by oral administration of amoxicillin and erythromycin. Similar to this regimen, the Brazilian Ministry of Health (MOH) recommends the use of ampicillin followed by amoxicillin and a single oral dose of azithromycin.

Category 3: Prenatal corticosteroids

Prenatal corticosteroid administration has been shown to reduce perinatal and neonatal mortality, the occurrence of RDS and the need for ventilatory support, the incidence of intraventricular hemorrhage, necrotizing enterocolitis, systemic infections in the first 48 hours of life, and to decrease rates of neonatal ICU admissions[2,8,18].

According to the evidence found in the literature[2,4,18], a single course of corticosteroids is therefore recommended for pregnant women between 24- and 34-weeks of gestational age at risk of preterm delivery. The annual report of the Committee on Perinatology and the Japanese Society of Obstetrics and Gynecology[9] reported its use both for the above situations, and in cases of suspected intrauterine infection, when indicated, in pregnancies between 22 and 34 weeks.

The recommended corticosteroid regimens are betamethasone (12 mg), intramuscularly, in two doses 24 hours apart, or dexamethasone (6 mg), intramuscularly, in four doses 12 hours

apart[11,18]. A study comparing the two recommended corticosteroids found no differences between them[18].

These recommendations agree with those made by the Ministry of Health[13] and Febrasgo's clinical protocol[1]. However, the national commission specialized in prenatal care of Febrasgo[1] recommends that before starting corticosteroid therapy the possibility of frank chorioamnionitis should be ruled out, since corticotherapy induces an increase in leukocytes, making it difficult to diagnose chorioamnionitis by this criterion.

Regarding the administration of repeated doses of corticosteroids, there is still insufficient evidence to support this practice[18]. The Guide to Clinical Practice of the Colombian Journal of Obstetrics and Gynecology[4] carries the recommendation that a single rescue dose can be administered to patients who have already received a full cycle, remain at risk of preterm labor 7 days or more after the initial dose, and remain with a gestational age of less than 34 weeks.

Category 4: Use of tocolytics

Among the methods found in the literature for preventing preterm birth, the use of tocolytics was the most found, even with many divergences among the studies regarding its recommendation. Most of the articles included in this review[2,4,19-21] do not recommend its use because, despite prolonging pregnancy, it did not show beneficial effects on maternal and perinatal outcomes, besides increasing the risk of chorioamnionitis. A review of the literature[8], published in 2015, concluded that the administration of tocolytic agents could be considered only in the short term, in the absence of intrauterine infection, for 24 to 48 hours, to allow the administration of a course of corticosteroids in pregnant women at risk of preterm delivery. A study comparing the various types of tocolytics[21], showed that Atosiban (oxytocin receptor antagonist) and nifedipine (calcium antagonist) are the tocolytics that have the best risk-benefit profile, with fewer maternal adverse effects, and are considered tocolytics of first choice. However, another study comparing the effect of nifedipine with placebo, showed no significant beneficial effects on prolongation of pregnancy and perinatal outcomes from its administration[17]. The different types of existing tocolytics have equal efficacy and various maternal and fetal adverse effects, and these should be considered when choosing for administration[21]. The Guide for Clinical Practice of the Colombian Journal of Obstetrics and Gynecology[4] does not recommend its use for women with PMR at any gestational age, because it is associated with Apgar scores below 7 at the fifth minute, increased need for neonatal ventilation and increased risk of chorioamnionitis. The evidence found agrees with the Febrasgo Clinical Protocol, which does not recommend the use of tocolytic agents to prevent preterm birth and cites the risk of an installed infectious condition in which the contractions presented as the first sign would be inhibited by tocolysis[1].

Progesterone has also been studied as a possible pharmacological agent in the prevention of preterm birth. One study evaluated the administration of progesterone suppositories and found that it was effective in delaying labor only in pregnancies between 28 and 30 weeks gestational age[22]. Another study evaluated the efficacy of 17 hydroxyprogesterone caproate but found no evidence of beneficial effects and therefore did not recommend its use[19]. Two studies included in this review do not provide sufficient evidence as to its efficacy and safety to make a recommendation.

Category 5: Recommendations regarding the use of magnesium sulfate

Little evidence was found in the literature regarding the use of magnesium sulfate in pregnant women with PPROM. However, recommendations from the American College of Obstetricians and Gynecologists (ACOG)[2] and the Guide for Clinical Practice of the Colombian Journal of Obstetrics and Gynecology (Revista Colombiana de Obstetrícia e Ginecologia)[4] were included in this review, which state that pregnant women with PROM at gestational age less than 32 weeks should receive magnesium sulfate for fetal neuroprotection, since its use has been associated with reduced risk of cerebral palsy. Despite this recommendation, the best therapeutic regimen has not yet been clarified[2]. In contrast to this evidence, the Febrasgo Clinical Protocol and the Ministry of Health do not provide information about its use in cases of PPROM.

Category 6: Performance of amniocentesis

The performance of amniocentesis in pregnant women with is also not well clarified, with little evidence regarding its efficacy, safety, and indications. A study conducted in Japan[10] showed that 10 to 15% of institutions perform amniocentesis, and it is indicated in cases of clinical findings of intrauterine infection. The other studies reinforce that its practice in the routine of care in cases of PPROM is not recommended, however, it is considered by some professionals to prove fetal lung maturity in pregnancies between 32 and 34 weeks[4,8], or to confirm suspicion of intrauterine infection[4]. The American College of Obstetricians and Gynecologists (ACOG)[2] does not bring evidence about indications for its performance in the cases cited above, appearing only as an indication for diagnosis of genetic diseases in the second trimester and relating it to the occurrence of PROM after its performance.

Concluding remarks

This integrative literature review allowed the analysis of recent evidence that answers the question about what the ideal conduct would be to take in case of premature rupture of ovular membranes in pregnancies between 28 and 34 weeks of gestational

age and showed that expectant management is the predominant recommendation in the literature, with constant monitoring of the pregnant woman and fetus. When 34 weeks is reached, depending on the clinical conditions of the mother-fetal binomial and on the quality of the nursery and neonatal ICU of each service, the expectant management or induction of labor can be continued, and the risks and benefits of each conduct should be considered and informed to the pregnant woman. For inducing labor, the recommendations are in case of signs and symptoms of premature rupture of membranes, pre-eclampsia, intrauterine growth restriction, fetomaternal alloimmunization or intrahepatic cholestasis, with PGE2, oxytocin or misoprostol being the indicated drugs. For maturation of the cervix PGE1 or PGE2, via the vaginal route, are effective.

Prophylactic antibiotic therapy is recommended, there is no standard regimen, but the Ministry of Health recommends its use[15] for seven days due to its beneficial effects on gestation and maternal and fetal outcomes. Corticosteroids have been shown to reduce complications resulting from prematurity and are recommended. Most services have recommended the use of a single cycle of corticosteroids, preferably Betamethasone (12 mg IM in two doses, 24 hours apart), between 24 and 34 weeks[1].

It is emphasized that administration of tocolytics and the performance of amniocentesis is not recommended.

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