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ORIGINAL PAPER

MATERNAL RISK FACTORS FOR CHORIOAMNIONITIS IN PRETERM NEONATES BORN BEFORE 34 WEEKS: A GESTATIONAL AGE–ADJUSTED ANALYSIS

Liuba DASCALIUC[1,2]✉, Anastasia CUPCEA[2], Ludmila OCLANSCHI[1,2], Adrian ROTARI[1], Lilia ROMANCIUC[1,2], Angela CRACEA[1], Ninel REVENCO[1,2], Larisa CRIVCEANSCAIA[1,2]

[1] Department of Pediatrics, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2] Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova

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Abstract

Introduction. Chorioamnionitis is an intra-amniotic infection associated with adverse neonatal outcomes, particularly in preterm newborns. Infants born before 34 weeks of gestation are at a higher risk of pulmonary complications, sepsis, and neurological impairments. Identifying maternal risk factors for chorioamnionitis is crucial for early intervention and improved neonatal prognosis.
The objective of the study was to identify maternal risk factors contributing to the development of chorioamnionitis in preterm newborns under 34 weeks of gestation.
Material and methods. This prospective cohort study included preterm neonates admitted to the Neonatal Intensive Care Unit (NICU) from Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova, between October 2023 and July 2024, following ethics committee approval. Eligible participants were grouped based on the presence of chorioamnionitis. Maternal medical records were reviewed for risk factors, including prolonged rupture

Résumé

Les facteurs de risque maternels de chorioamnionite chez les nouveau-nés prématurés nés avant 34 semaines: une analyse ajustée en fonction de l'âge gestationnel

Introduction. La chorioamnionite est une infection intra-amniotique liée à des complications néonatales, en particulier chez les nouveau-nés prématurés. Les nourrissons nés avant 34 semaines d'aménorrhée présentent un risque accru de complications pulmonaires, de sepsis et de troubles neurologiques. L'identification des facteurs de risque maternels de chorioamnionite est essentielle pour une intervention précoce et un meilleur pronostic néonatal.
L'objectif de l'étude a été d'identifier les facteurs de risque maternels contribuant au développement d'une chorioamnionite chez les nouveau-nés prématurés de moins de 34 semaines d'aménorrhée.
Matériel et méthodes. Une étude prospective de cohorte a été menée entre octobre 2023 et juillet 2024 sur des prématurés admis à Unité de Soins Intensifs

✉ Address for correspondence: Liuba DASCALIUC
Department of Pediatrics, Nicolae Testemitanu State University of Medicine and Pharmacy, Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova
Email: liuba.dascaliuc@usmf.md; Phone: +373 60575901

of membranes, premature labour, maternal infections, and obstetric complications. Statistical analysis included chi-square tests and logistic regression, adjusting for confounders such as gestational age.

Results. The study included 108 preterm newborns, of whom 50% were diagnosed with chorioamnionitis. Maternal factors significantly associated with chorioamnionitis included prelabor rupture of membranes (PROM) >18 hours ($p<0.001$), meconium-stained amniotic fluid ($p=0.002$). The newborns most affected were those born at less than 28 weeks of gestation ($p<0.05$). When adjusted for gestational age, PROM >18 hours seems to be an independent factor for chorioamnionitis (CA) ($p<0.001$).

Conclusions. PROM >18 hours and meconium-stained amniotic fluid (MSAF) are key risk factors for chorioamnionitis in preterm newborns. Early identification and management of these factors may reduce neonatal morbidity and improve outcomes in this vulnerable population.

Keywords: preterm newborns, chorioamnionitis, PROM, risk factors.

List of abbreviations:
BPD – bronchopulmonary dysplasia
CA – chorioamnionitis
CCA – clinical chorioamnionitis
FIRS – fetal inflammatory response syndrome
HCA – histological chorioamnionitis
IUGR – intrauterine growth restriction
MSAF – meconium-stained amniotic fluid
NICU – Neonatal Intensive Care Unit
PROM – prelabour rupture of membranes
RDS – respiratory distress syndrome
TORCH – toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, herpes simplex virus
UTI – urinary tract infections

Néonatals, Établissement Public de Santé – Institut de la Mère et de l'Enfant, Chisinau, République de Moldova, après approbation éthique. Les participants ont été divisés en deux groupes selon la présence ou l'absence de chorioamnionite. Les dossiers médicaux maternels ont été examinés afin de rechercher les facteurs de risque, notamment la rupture prolongée des membranes, le travail prématuré, les infections maternelles et les complications obstétricales. L'analyse statistique comprenait des tests du khi carré et une régression logistique, avec ajustement des facteurs de confusion tels que l'âge gestationnel.

Résultats. Sur 108 nouveau-nés, 54 nouveau-nés ont été exposés à une chorioamnionite. Les facteurs maternels significativement associés à la chorioamnionite comprenaient une rupture prématurée des membranes (RPM) > 18 heures ($p < 0,001$) et un liquide amniotique méconial ($p = 0,002$). Les nouveau-nés les plus touchés étaient ceux nés à moins de 28 semaines d'aménorrhée ($p < 0,05$). Après ajustement pour l'âge gestationnel, une RPM > 18 heures semble être un facteur indépendant de chorioamniotite ($p < 0,001$).

Conclusions. Une RPM > 18 heures et une liquide amniotique teinté de méconium sont des facteurs de risque majeurs de chorioamnionite chez les nouveau-nés prématurés. Leur identification et leur prise en charge précoces pourraient réduire la morbidité néonatale et améliorer les résultats dans cette population vulnérable.

Mots-clés: nouveau-nés prématurés, chorioamnionite, rupture prématurée des membranes, facteurs de risqué

Introduction

Chorioamnionitis (CA) is a serious intra-amniotic infection that affects the placenta, fetal membranes, and amniotic fluid, posing significant risks to both the mother and the newborn. It is commonly associated with preterm labor and delivery, particularly in pregnancies that end before 34 weeks of gestation. Preterm newborns are highly vulnerable to complications due to CA, including neonatal sepsis, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular haemorrhage, and long-term neurodevelopmental impairment[1,2]. Given these risks, understanding the maternal factors contributing to the development of CA is essential for improving neonatal outcomes and implementing preventive strategies.

The pathophysiology of CA involves an ascending infection from the lower genital tract, typically caused by bacteria such as *Escherichia coli*, *Group B Streptococcus*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*[3,4]. These pathogens can invade the amniotic sac, triggering an inflammatory response that compromises foetal well-being. The inflammatory cascade initiated by CA can lead to prelabour rupture of membranes (PROM), increased uterine contractions, and early labour, all of which contribute to preterm birth[5]. Moreover, the presence

of pro-inflammatory cytokines and bacterial toxins in the amniotic fluid can adversely affect fetal lung and brain development, increasing the risk of perinatal morbidity and mortality[6].

Several maternal risk factors have been identified as contributing to the onset of chorioamnionitis, with PROM being one of the most significant. When the protective barrier of the amniotic sac is compromised for an extended period—generally more than 18 hours—the risk of ascending bacterial infection increases substantially[7]. Other maternal factors include bacterial vaginosis, urinary tract infections (UTIs), previous preterm births, frequent digital cervical examinations during labour, and the presence of meconium-stained amniotic fluid (MSAF)[8,9]. Additionally, certain demographic and lifestyle factors, such as young maternal age, low socioeconomic status, and smoking, have been linked to an increased likelihood of intra-amniotic infection[10].

The impact of CA on neonatal health is profound. Preterm newborns affected by CA are at heightened risk for early-onset neonatal sepsis, a life-threatening condition that requires immediate antibiotic therapy and intensive care management[11]. Additionally, the inflammation associated with CA can disrupt fetal lung maturation, predisposing infants to RDS and prolonged ventilatory support[12]. There is also growing evidence that intrauterine inflammation plays a role in the development of periventricular leukomalacia and cerebral palsy, highlighting the long-term neurodevelopmental consequences of this condition[13,14].

Despite the well-established risks associated with CA, early identification and prevention remain challenging. Screening for maternal infections, timely administration of antibiotics, and careful monitoring of pregnancies complicated by PROM are key strategies for reducing the incidence of this condition[15]. However, gaps remain in our understanding of the interplay between maternal risk factors and neonatal outcomes, necessitating further research to refine clinical guidelines and intervention protocols.

The objective of the study was to identify maternal risk factors contributing to the development of CA in preterm newborns under 34 weeks of gestation.

Material and methods

This prospective cohort study included preterm neonates admitted to the Neonatal Intensive Care Unit (NICU), Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova, between October 2023 – July 2024.

The patients` parents signed a written consent to participate in the study. The study was approved by the Ethics Committee (approval number 72, October 28, 2022). The study included 108 infants less than 34 weeks of gestation.

The inclusion criteria were as follows: preterm newborns less than 34 weeks of gestation, born in this hospital, admitted to NICU in the mentioned period.

The exclusion criteria were as follows: preterm newborns over than 34 weeks of gestation, with congenital malformations incompatible with life.

Subjects were divided into two groups: (1) In the basic group there were selected 54 newborns from mother with CA; (2) The control group included 54 preterm infants less than 34 weeks of gestation without CA. For diagnoses of CA we used the criteria adopted from American College of Obstetricians and Gynecologists (ACOG) 2017: maternal temperature greater than or equal to 39.0°C or when the maternal temperature is 38.0–38.9°C and one additional clinical risk factor is present[16].

Clinical data were extracted from medical records. The subjects were categorized based on gestational age and birth weight, as described in medical literature[17]. Gestational age classification included: (a) extremely preterm (<28 weeks), (b) very preterm (28–32 weeks), and (c) moderate preterm (32–34 weeks).

Data were collected to an Excel database and included demographic data, maternal risk factors and presence of clinical and/or histological CA. Analysed maternal risk factors were history of preterm birth, abortions, stillbirths, amniotic sac infection, fever during labour, intrauterine growth restriction (IUGR), oligohydramnios, PROM >18 hours, MSAF, TORCH, anaemia, preeclampsia, c-section. The presence of clinical CA (CCA) was based on maternal fever and the presence of one of the risk factors: maternal tachycardia (>100 beats per minute), fetal tachycardia (>160 beats per minute), uterine tenderness on palpation, the presence of purulent or foul-smelling amniotic fluid, maternal leukocytosis (>15,000/mm^3 in the absence of corticosteroid therapy), PROM >18 hours. Histological CA was related to the presence of neutrophilic infiltration within the fetal membranes and umbilical cord.

Obtained data were analysed using statistical tools. Statistical analysis involved chi-square tests to determine if there is association between maternal risk factors and CA. Logistic regression was used to assess the association between maternal risk factors and CA, adjusting for potential confounders such as gestational age. A p-value <0.05 was considered statistically significant.

Table 1. Distribution of gestational age categories by chorioamnionitis status in the preterm cohort

Term of gestation	CA		*Control*		*Total*	
	n	%	n	%	n	%
<28 weeks	**14***	25.9	6	11.1	20	18.5
28-32 weeks	31	57.4	31	57.4	62	57.4
>32 weeks	9	16.7	17	31.5	26	24.1
Total	54	100.0	54	100.0	108	100.0
Abbrev.	*$p<0.05$					

Table 2. Gender distribution of preterm newborns by chorioamnionitis status

Gender	CA		*Control*		*Total*	
	n	%	n	%	n	%
Female	26	48.1	32	59.3	58	53.7
Male	28	51.9	22	40.7	50	46.3
Total	54	100.0	54	100.0	108	100.0

Table 3. Maternal obstetric and infectious risk factors and their association with chorioamnionitis

Maternal obstetric and infectious risk factors	CA		*Control*		*Total*	
	n (54)	%	n (54)	%	n (108)	%
History of preterm birth	8	14.8	6	11.1	14	13.0
Abortions	20	37.0	14	25.9	34	31.5
Stillbirths	5	9.3	1	1.9	6	5.6
Amniotic sac infection	29	53,7	0	0.0	29	26.9
Fever during labor	3	5.6	0	0.0	3	2.8
IUGR	9	16.7	12	22.2	21	19.4
Oligohydramnios	13	24.1	7	13.0	20	18.5
PROM >18 hours ($p<0.001$)	***36**	66.7	12	22.2	48	44.4
MSAF ($p=0.002$)	***11**	20.4	1	1.9	12	11.1
TORCH	5	9.3	1	1.9	6	5.6
Anemia	28	51.9	25	46.3	53	49.1
Preeclampsia	15	27.8	16	29.6	31	28.7
C-section	30	55.6	36	66.7	66	61.1

*$p < 0.05$

Results

We performed a prospective cohort study, which involved 108 preterm infants less then 34 weeks of gestation admited to the NICU of the Mother and Child Institute, Chisinau, between October 2023 and July 2024. The subjects were divided into two groups based on the presence of CA. The study group involved 54 subjects born to mothers with clinical and/or histological CA. The control group involved 54 subjects born to mothers without evidence of CA. For further analyses, we stratified the study population according to gestational age. We compared gestational ages of preterm neonates in the CA and control group (Table 1). The findings shows that the largest proportion of infants (57.4%) in both groups are very preterm. Among infants born at less than 28 weeks, the incidence of CA was significantly higher in the CA group compared to the control group (25.9% vs 11.1%), indicating a potential association between CA and extremely preterm birth ($p<0.05$). The proportion of infants born after 32 weeks of gestation was higher in the control group compared to the CA group (31.5% vs 16.7%). The results highlight the differences in the distribution of gestational age between the two groups, with a notable trend toward earlier gestational ages in the CA group.

Gender distribution of the subjects in the CA and control group is presented in Table 2. The proportion of male infants was higher in the CA group compared to the control group (51.9% vs 40.7%), suggesting some differences in gender distribution between the groups, although there is no strong statistical evidence

Table 4. Maternal risk factors stratified by gestational-age category in the overall cohort

Maternal risk factors	*Term of gestation*							
	<28 weeks		*28-32 weeks*		*32-34 weeks*		*Total*	
	n (20)	%	n (62)	%	n (26)	%	n (108)	%
History of preterm birth	3	15.0	8	12.9	3	11.5	14	13.0
Abortions	6	30.0	20	32.3	8	30.8	34	31.5
Stillbirths	2	10.0	3	4.8	1	3.8	6	5.6
Amniotic sac infection (p=0.014)	***10**	50.0	16	25.8	3	11.5	29	26.9
Fever during labor	2	10.0	1	1.6	0	0.0	3	2.8
IUGR	2	10.0	12	19.4	7	26.9	21	19.4
Oligohydramnios	7	35.0	11	17.7	2	7.7	20	18.5
PROM >18 h (p=0.006)	***14**	70.0	28	45.2	6	23.1	48	44.4
MSAF (p=0.012)	***6**	30.0	4	6.5	2	7.7	12	11.1
TORCH	2	10.0	2	3.2	2	7.7	6	5.6
Anemia	14	70.0	28	45.2	11	42.3	53	49.1
Preeclampsia	3	15.0	22	35.5	6	23.1	31	28.7
C-section (p=0.002)	***6**	30.0	39	62.9	21	80.8	66	61.1

*$p< 0.05$

Table 5. Predictors of chorioamnionitis in preterm newborns: adjusted odds ratios from logistic regression models

Predictor	*PROM >18 h (aOR, 95% CI)*			*MSAF (aOR, 95% CI)*			*Both predictors entered together (aOR, 95% CI)*		
	β	p	aOR	β	p	aOR	β	p	aOR
Gestational age (per week)	-0.191	0.027	0.826	-0.230	0.006	0.795	-0.172	0.54	0.842
PROM >18 h (yes vs no)	1.724	<0.001	5.608	–	–	–	1.577	0.001	4.838
Meconium-stained AF (yes vs no)	–	–	–	2.320	0.032	10.172	1.846	0.970	6.332

β = log-odds coefficient; aOR = adjusted odds ratio; GA entered as a continuous covariate (per 1-week increase). "–" = predictor not included in that model.

to suggest that gender distribution is influenced by CA in this sample.

To achieve the objective of the study, we focused on maternal risk factors (Table 3). Our analysis revealed that preterm PROM was significantly more frequent in the CA group (66.7% vs. 22.2%; χ^2 = 21.6, p < 0.001), suggesting a good corelation between PROM > 18 hours and CA. The CA group also showed a significantly higher occurrence of MSAF (20.4% vs. 1.9%; χ^2 = 9.38, p = 0.002). According to these data, we understand that CA has some clinical signs which may increase accuracy of its diagnosis.

In our study, we also found that a maternal history of preterm birth was more prevalent in the CA group (14,8% vs 11,1%), as well as abortion (37.0% vs 25.9%), but there's no significant statistical difference. Stillbirths occurs in 5.6% with a higher incidence in CA group (9.3% vs 1.9%). The incidence of amniotic sac infection is high in our population (26.9%), but there is no possible to compare because all the subjects are from CA group. Also, we found fever in mother only in 5.6% in CA group.

When we stratified our cohort by gestational age (Table 4), we saw some statistically significant differences between groups. In extremely preterm newborns we found a higher presence of amniotic sac infection compared to very preterm and moderate preterm newborns (50% vs 25.8% vs 11.5%) (p=0.014), PROM >18 h (70% vs 45.2% vs 23.1%) (p=0.006), MSAF (30% vs 6.5% vs 7.7%) (p=0.012). Also, we observed that c-section was significant lower in extremely preterm newborns compared to very preterm and moderate preterm newborns (30% vs 62.9% vs 80.8%) (p=0.002), probable due to maternal benefits.

To understand the impact of these factors on CA in our subjects, we put them into a logistic regression model and adjusted for gestational age (Table 5).

In the gestational age–adjusted logistic regression analysis, PROM > 18 hours was significantly associated with an increased likelihood of CA. In the single-predictor model adjusted for gestational age, PROM > 18 hours had an adjusted odds ratio (aOR) of 5.61 (p <0.001). MSAF also showed a strong association in its single-predictor model (aOR = 10.17; p = 0.032). However, when both PROM > 18 hours and MSAF were entered into the same model, the effect of PROM remained elevated (aOR = 4.84), while the association for MSAF (aOR = 6.33) was no longer statistically significant (p = 0.970). Gestational age, modeled as a continuous variable, showed a protective trend (aOR = 0.84 per additional week). These findings suggest that PROM > 18 hours is an independent risk factor for CA, whereas the apparent effect of MSAF may be partly explained by its correlation with PROM.

Other maternal or pregnancy-related conditions observed in the study group included urogenital infections (with/without asymptomatic bacteriuria), placental implantation abnormalities, abnormal fetal presentation, varicose veins, hemolytic disease, COVID-19, and several rare obstetric or systemic disorders (e.g., HELLP syndrome, TORCH infections, placental abruption, cervical insufficiency, thrombophilia, endocrine disorders, epilepsy, syphilis). These factors were not included in the statistical analysis due to small subgroup sizes and inconsistent documentation, which could introduce bias.

Discussion

In this prospective cohort of preterm births <34 weeks of gestation, we found that PROM >18 hours remained independently associated with CA after adjustment for gestational age, whereas the association of MSAF was attenuated in multivariable models. These findings support the long-recognized link between prolonged membrane rupture and ascending intra-amniotic infection in early preterm gestations and emphasize the importance of accounting for gestational age as a confounder when estimating risk. Contemporary guidance underscores that intra-amniotic infection (IAI) is a major driver of acute neonatal morbidity and longer-term complications, and that diagnosis is based on standardized intrapartum criteria combining maternal temperature with clinical risk factors[18,19]. Our data align with this framework and quantify the risk attributable to PROM in a gestational age-adjusted models.

Multiple lines of evidence connect membrane rupture with microbial invasion of the amniotic cavity (MIAC) and intra-amniotic inflammation, particularly in early preterm labor. Classic and contemporary studies document that MIAC is common in early preterm parturition, and its prevalence rises with labor and with the duration of membrane rupture[20–22]. Clinical programs and implementation resources report high IAI rates in the setting of preterm labor or PROM (40–70%), depending on definitions and testing methodology. Our GA-adjusted association between PROM >18 hours and CA (aOR = 4.8) is consistent with these observations and with practice guidance that balances expectant management against infection risk in PPROM[19,24].

The role of MSAF in preterm birth is more nuanced. Although MSAF is classically associated with term/post-term gestation, several studies suggest that preterm MSAF is an ominous sign linked with CA, cord compression, and adverse maternal infectious outcomes[25–27]. A 2017 series reported preterm MSAF as a strong predictor of CA, recommending heightened surveillance and expedited delivery consideration[27]. More recently, analyses have again tied preterm MSAF to intrauterine inflammation and infectious morbidity[25,26]. In our cohort, MSAF showed a marked association in gestational age-adjusted single-predictor models but lost statistical independence when entered jointly with PROM. This pattern likely reflects collinearity and shared causal pathways (e.g., fetal stress during prolonged membrane rupture, intrauterine inflammation), as well as limited power to resolve independent effects in a modest sample.

The pathobiology connecting PROM, MIAC, and CA is well described. Ascending microorganisms, including *Ureaplasma spp.* and *Mycoplasm*a, are frequently identified in the amniotic cavity, placental tissues, or the preterm airway and have been associated with histologic CA and adverse neonatal outcomes[28–31]. Experimental and genomic work implicates *Ureaplasma* in driving intra-amniotic inflammation and preterm birth phenotypes in susceptible hosts[30]. Beyond culture-positive MIAC, "sterile" intra-amniotic inflammation is increasingly recognized and may perpetuate fetal injury through cytokine cascades even when bacteria are not isolated[32]. These mechanisms converge in the fetal inflammatory response syndrome (FIRS), which has been linked across systematic reviews and meta-analyses to worse neonatal outcomes[33]. Together, they provide a biologically coherent explanation for our clinical finding that the duration of membrane rupture, an exposure that facilitates microbial ascent and sustained inflammation, tracks with CA risk.

For pregnancies at <34 weeks of gestation with PROM, management necessarily weighs fetal maturity against infection. The ACOG Practice Bulletin on PROM outlines diagnostic principles and timing

of delivery in PROM, emphasizing infection surveillance, limited digital examinations, and timely antibiotics and delivery when infection is suspected[19,24]. In parallel, the 2024 ACOG Clinical Practice Update sharpened criteria for suspected IAI, operationalizing decision points that incorporate maternal temperature thresholds plus co-factors (e.g., leukocytosis, purulent cervical discharge, fetal tachycardia)[18]. Our data reinforce that PROM >18 hours itself is a quantifiable risk marker; embedding time-since-rupture into triage and escalation protocols may support earlier recognition and reduce exposure to prolonged intra-uterine inflammation. Given evolving evidence that CA exposure is associated with neonatal morbidities, particularly BPD, minimizing infectious burden before delivery remains a priority[30,32,33].

In summary, our gestational age-adjusted analysis highlights PROM >18 hours as an independent maternal risk factor for CA among births <34 weeks, while preterm MSAF appears to be a high-risk sign that overlaps with PROM-related pathways. These results support protocolized surveillance that couples latency duration with standardized IAI criteria to guide timely intervention in PPROM.

Conclusions

PROM and MSAF are key risk factors for CA in preterm newborns. Early identification and management of these factors may reduce neonatal morbidity and improve outcomes in this vulnerable population.

Authors' Contributions:

L.D., A.C., L.O., A.R., L.R., A.C., N.R., L.C. were responsible for clinical diagnosis, paraclinical investigations, treatment decisions, and follow-up of the patients. L.D., A.C., L.O., A.R., L.R., A.C., N.R., L.C. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patients included in the study."

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