Original Article

Comparison of Histological Chorioamnionitis in Pre-Term Delivery with and without Pre-Term Rupture of Membrane

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Abstract

Background: Histological chorioamnionitis (HCA) is a histologic response to intra-uterine inflammation that is usually confirmed by pathology examination after pre-term delivery and characterized by acute granulocyte infiltration into the fetal-maternal or fetal tissues. This study aimed to compare the HCA in pre-term delivery with and without pre-term rupture of membrane for assessment of its role on early neonatal outcomes and fetal heart rate patterns.

Materials and Methods: This case-control study was conducted on placenta, chorionamnion, and cord of 100 cases with and without pre-term rupture of membrane between 28 0/7 and 36 6/7 weeks delivered between March 2018 and February 2021. The kind of delivery, gestational age, neonatal intensive care unit admission, a 5 min Apgar score <7, and fetal heart rate patterns in two groups with and without HCA were assessed.

Results: The odds ratio (OR) for HCA was adjusted for fetal heart rate patterns, gestational age, and delivery mode (vaginal delivery or cesarean section). Vaginal delivery, gestational age, neonatal intensive care unit admission, and a 5 min Apgar score <7 were associated with HCA [OR: 2.4, 95% confidence interval (CI): 1.2–9.5, $P < 0.05$; OR: 0.8, 95% CI: 0.5–1.1, $P < 0.05$; OR: 1.1, 95% CI: 0.6–2.1, $P < 0.05$; and OR: 0.9, 95% CI: 0.7–1.3, $P < 0.05$), respectively. However, there were no specific fetal heart rate patterns associated with HCA.

Conclusion: Placental histology examination in pre-term infants with low Apgar scores may be useful to investigate the association between neonatal complications in pre-term delivery and asymptomatic chorioamnionitis.

Keywords: Chorioamnionitis, fetal, fetal membranes, heart rate, histology, pre-mature birth, pre-mature rupture

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Submitted: 29-Sep-2021; **Revised:** 17-May-2023; **Accepted:** 20-May-2023; **Published:** 27-Apr-2024

Introduction

Presentation of chorioamnionitis is of two types: One form of chorioamnionitis is clinical chorioamnionitis, indicated by fever and fetal or maternal tachycardia uterine tenderness. The rise of ESR CRP and leukocytosis with neutrophil shift is an indication of urgent delivery.[1,2] Another form of chorioamnionitis is histological chorioamnionitis (HCA), which may be devoid of symptoms.[3,4] HCA is a histologic response to intra-uterine inflammation that is usually confirmed by pathology examination after pre-term delivery and characterized by acute granulocyte infiltration into the fetal-maternal or fetal tissues;[5] it is often seen in pre-term delivery, and the ethology is unknown. Chorioamnionitis can be chronic, subacute, or acute.[6] Chorioamnionitis can be acute before labor, during labor, after delivery, or during post-mortem. Chorioamnionitis most commonly is associated with prolonged rupture of membrane multiple vaginal exams, especially after post-rupture of membrane meconium-stained fluid and non-case pregnant women with bacteria or viral infection.[7] Pre-term birth is a

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_300_21

How to cite this article: Shahshahan Z, Zarean E, Jahanfar S, Hedayat P. Comparison of histological chorioamnionitis in pre-term delivery with and without pre-term rupture of membrane. Adv Biomed Res 2024;13:33.

delivery less than 37 weeks. Pre-term birth is a major cause of perinatal mortality and long-term morbidity, including periventricular leukomalacia, bronchopulmonary dysplasia, pneumonia, cerebral palsy hypoglycemia, and fetal gundis.[8]

Materials and Methods

This case-control study was conducted from March 2018 to February 2021 in Alzahra Hospital, Isfahan, Iran. After approval from the ethics committee of Isfahan University of Medical Sciences, the placenta, chorion, amnion, and umbilical cord of 100 singleton fetus pregnant women with and without pre-term rupture of membrane between 28 0/7 and 36 6/7 weeks were assessed for HCA by a pathologist. The exclusion criteria were multiple pregnancies, obstetric complications including preeclampsia, placenta abration, placenta previa, fetal growth restriction, fetal and cord anomaly, maternal complications, intra-uterine fetal death, and Rhesus (Rh) immunization. All aspects of the study were described for participants, but formal consent for this type of study is not required. After assessment of placenta, chorion, amnion, and cord, we studied HCA in pre-term delivery with and without pre-term rupture of membrane on early neonatal outcomes and fetal heart rate patterns.

Maternal and neonate characteristics

The gestational age was between 28 0/7 and 36 6/7 weeks and determined based on menstrual last period (LMP). If there is regular menstruation or ultrasound under 20 weeks and if the results of the two methods are more than 7 days with the same difference, ultrasound results were accepted. Maternal background information included delivery, height, pre-pregnancy weight, and delivery weight. Neonatal outcomes included birth weight, birth height, umbilical artery pH, 1 and 5 minute Apgar scores, placental weight, umbilical cord length, maximum umbilical cord diameter, and neonatal intensive care unit (NICU) admission.

Methods of delivery were classified as normal vaginal delivery and elective cesarean section. The cesarean section was performed only for abnormal presentation or previous cesarean section. The placental weight, umbilical cord length, and maximum umbilical cord diameter were measured immediately after delivery by a trained mid-wife.

In the pathology department, histological examination of the placenta, chorion, and umbilical cord was performed by a pathologist based on the severity of inflammation according to Blanc classification (Blanc).[9] Accordingly, the cases were divided into two groups. The group with HCA was considered as a control group. Before multivariate logistic regression, infant information and maternal background information were compared between the two groups.

Fetal heart rate pattern

Fetal heart rate patterns taken 1–2 hours before delivery were reviewed in the past with the advice of a perinatologist approved by the University of Isfahan without any knowledge of neonatal results and histological results.

Tachycardia was referred to as a baseline FHR of more than 160 beats per minute. Patterns of FHR deceleration were classified into variable deceleration (VD), prolonged deceleration (PD), and late delay (LD). Prolonged deceleration was defined as the apparent visual reduction to >15 beats per minute from baseline for ≥2 min but less than 10 min. Recurrent late deceleration was defined as late deceleration associated with more than 50% of uterine contraction. VD was classified into three categories: mild, moderate, and severe (mild: variable reductions that did not have moderate or severe criteria; moderate variable decline: <70 beats per minute and 30–60 seconds duration or 70–80 beats per minute in duration >60 seconds; severe 60 seconds and <70 beats per minute) were among the most widely used patterns for this classification. PD was defined as the apparent visual reduction to ≥15 beats per minute from baseline for ≥2 min but less than 10 min. Recurrent LD was defined as LD associated with more than 50% of uterine contractions.[10-12]

Statistical methods

Neonatal outcomes, maternal information, and fetal heart rate patterns were compared between HCA with and without rupture of membrane and non-HCA with and without rupture of membrane. Then, multivariate logistic regression models were used to determine whether FHR patterns or maternal backgrounds were related to HCA. Criteria for entering variables for this model were determined by clinical significance and univariate analysis. SPSS version 21 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Depending on whether the data were normally or abnormally distributed, t-test was performed and Chi-square test was used to compare the classified variables. The statistically significant level was determined as $P < 0.05$.

Results

During the period of study, there were 237 deliveries, and 167 cases were delivered between 28 0/7 and 36 6/7 weeks. Among the 167 cases delivered between 28 and 36 weeks of gestational age, 12 cases presented with fetal anomalies. There were 16 cases with multiple pregnancies; 13 cases of fetal growth restriction; 14 cases with obstetric complications including preeclampsia, abruption, and placenta previa; eight cases with elective delivery because of maternal complications, two cases with intra-uterine fetal death, and two cases with Rh iso-immunization; out of 100 cases, 48 had HCA and 52 did not have HCA.

Maternal characteristics

There were no significant differences regarding maternal age, parity, and body mass index (BMI) ($P = 0.21$, $P = 0/09$, and $P = 0/10$, respectively); vaginal delivery and a low gestational age were more common in the histological CAM group ($P < 0.05$). An early pre-term gestational age was more

common in PROM with HCA, but vaginal delivery had no significant difference in PROM with HCA compared to PROM without HCA.[Table 1]

Neonatal characteristics

There was no significant difference in birth weight between groups ($P = 0.65$) and in the umbilical arterial pH ($P = 0/38$). Although cord length and placental weight were not significantly different ($P = 0.21$ and $P = 0.14$, respectively), in the histological CAM group, the cord diameter was higher (control, 1.2 ± 0.3 cm vs. histological CAM, 1.5 ± 0.5 cm, $P < 0.05$).[Table 2]

There was a significant difference in the proportion of 5-minute Apgar scores less than 7 and NICU admission ($P < 0.05$). This study showed that early vaginal delivery was significantly and independently associated with HCA [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.2, 95% $P < 0,05$]. The results were similar in comparison of PROM group with HCA and PROM with normal pathology.[Table 3]

FHR pattern

The recurrent LD was more common in the control group ($P < 0/05$).

There were no significant differences between the two groups in terms of proportion of tachycardia and variable deceleration as well as deceleration (control 8/9% vs. histological CAM 18/7%, $P = 0.09$), decreased variability (control 5.7% vs. histological CAM 8.3%, $P = 0/78$), and mild VD (control 38.4% vs. histological CAM 47.9%, $P = 0.09$); the presence of deceleration was not significantly different between the two groups (control 48.1% vs. histological CAM 66.6%, $P = 0.09$), but vaginal delivery had no significant difference in PROM with HCA compared to PROM without HCA. [Table 4]

Factors suggesting histological CAM

This study showed that vaginal delivery had a significant and independent association with histological CAM (OR: 2.4, 95% CI: 1.2–9.5, $P < 0.05$). 7 was associated with histological CAM (OR: 1.1, 95% CI: 0.6–2.1, $P < 0.05$ and OR: 0.9, 95% CI: 0.7–1.3, $P < 0.05$). Conversely, LD recurrence and a higher gestational age were independent and important factors associated with lower risk of histological CAM (OR: 0.3, 95% CI: 0.03–0.92, $P < 0.05$ and OR: 0.7, 95% CI: 0.5–0.9, $P < 0.05$, respectively).

Table 1: Maternal backgrounds of the two groups

Variables	Control *n*=52	Histological CAM *n*=48	*P*
Age, years (mean±SD)	27/8±4	26/7±3	0.21
Pariety	1.9±0/9	1.1± 0/9	0.09
Gestational age, weeks (mean±SD)	33/9±2	31/13±2	<0.05
Height, cm (mean±SD)	162±4	161±3	0.27
BMI at delivery, kg (mean±SD)	25/7±4/9	27/8±5/5	0.10
Vaginal delivery (%)	26/9	41/6	<0.05

Table 2: Neonatal outcomes of the two groups

	Control *n*=52	Histological CAM *n*=48	*P*
Birth weight, g (mean±SD)	2231±560	2152±380	0.65
NICU Admission	13.4	43.7	<0.05
Birth height, cm (mean±SD)	48±5	45±5	0.18
Umbilical arterial pH (mean±SD)	7.32±0.07	7.29±0.09	0.38
5-min Apgar score <7 (%)	5.7	20.8	<0.05
Placenta weight, g (mean±SD)	489/4±13	491/7±13	0.14
Cord length, cm (mean±SD)	46±15	45±10	0.21
Cord diameter, cm (mean±SD)	1.3±0.4	1.6±0.5	<0.05
Male (%)	50	52.1	0.53

Table 3: Different FHR patterns 1–2 hours before delivery in the two groups

FHR pattern (%)	Control *n*=52	Histological CAM *n*=48	*P*
Tachycardia	7.69	16.6	0.08
Decreased variability	5.7	8.3	0.78
Deceleration	48.1	66.6	0.09
Mild VD	38.4	47.9	0.09
Moderate VD	42.3	45.8	0.69
Severe VD	19.2	12.5	0.51
Recurrent LD	17.3	6.2	<0.05

FHR, fetal heart rate; VD, variable deceleration; PD, prolonged deceleration; LD, late deceleration

Table 4: Comparing the early neonatal outcomes in PROM with and without HCA

Neonatal outcomes	Control *n*=35 PROM without HCA	Case *n*=37 PROM with HCA	*P*
GA (week) mean±SD	32.04±1	29.06±1	<0.05
NVD (%)	62.85	54	0.78
Abnormal FHR (%)	60	67.5	0.86
NICU (%)	14.3	37.83	<0.05
Apnea (%)	2.85	21.62	<0.05
ABG PH mean±SD	7.31±0.07	7.23±0.09	<0.05
5 min APGAR <7	5.7	16.2	<0.05

GA (gestational age), NVD (normal vaginal delivery), FHR (fetal heart rate), NICU (neonatal intensive care unit), ABG (arterial blood gas)

Discussion

Based on this study, it was that among women of pre-term labor between 28 and 36 weeks of gestation, gestational age was associated with histological CAM. Contrary to our expectations, recurrent LD, which is a sign of decreased blood flow during uterine contractions, is independently associated with a reduced risk of histological CAM.

It also showed that the FHR pattern was not a reliable indicator for histological diagnosis of CAM because the FHR pattern was CAM histological in most cases. Although some researchers have shown an association between clinical CAM and abnormal FHR patterns such as tachycardia 7-8, decreased diversity 7-9, and decreased speed 9-10, these results are

ambiguous.[13] Hyo Kyozuka[14] reported that no association was found between histological CAM and abnormal FHR patterns, indicating hypoxia status. Hidehiko Miyake *et al*.[15] examined the association of an abnormal FHR pattern for predicting perinatal infection (CAM, neonatal sepsis, and neonatal pneumonia), but it was not useful because of its low sensitivity (46%; 95% specificity). Buhimschi *et al.* reported that fetuses with severe intra-amniotic inflammation were more likely to have some changes, but not all FHR-MPs changed. Interestingly, the most specific changes (increase in baseline FHR compared to non-inflammatory cases and a non-reactive and unreliable FHR-MP) at the time of IEV were because of an increase in the proportion of embryos that were non-reactive and/or reactive. They gave near-delivery reassuring patterns. However, increased AF inflammatory status could not independently explain the possible association between abnormal FHR.[16]

The results of this study are consistent with the results of previous studies in pre-term infants or in animal models. Failure to diagnose pre-term HCA confuses obstetricians and complicates clinical decision making.[17] Diagnosis of CAM is usually with clinical signs before delivery (clinical CAM), and histological CAM determines the microbial evidence in the amniotic fluid and histopathological findings after delivery. Methods of CAM diagnosis and management of pre-term delivery using FHR monitoring vary depending on the institution. In the present study, histological cases of CAM were used using the standard method of pathological examination of the placenta and umbilical cord.[5]

In a study by Priyanka Goradia *et al*.,[18] they reported that DREAM (downstream regulatory element antagonist medulator) significantly increased in fetal membranes after pre-term delivery and amniosis with pre-mature tissue chorioamnionitis compared with amniosis without pre-mature tissue chorioamnionitis. DREAM plays a role in the development of IL-1-mediated proliferative and proliferative mediators, leading to pre-term labor in early pregnancy. Our study shows that an early gestational age, NICU admission, and an Apgar score of 5 minutes less than 7 are related to histological CAM.[18,19]

In another study, the prevalence of clinical chorioamnionitis and HCA was 8.3% and 23.2%, respectively. The HCA frequency in mothers of less than 32 weeks and less than 30 weeks was 47.3% and 83.3%, respectively. In mothers with HCA, infants had significantly lower Apgar scores and higher SNAP-PE-II and CRIB scores with increased need for mechanical ventilators and surfactants[20] and CAM is also associated with an increased incidence of pre-mature membrane rupture and pre-term delivery.[21]

Paul J. Wendel *et al*.[22] reported that there was no difference in umbilical cord pH, Apgar score, sepsis, neonatal admission, and neonatal oxygen demand based on the distance between the diagnosis of chorioamnionitis and delivery. None of the neonates had abnormal fetal acidosis (Ua pH <7.00) in our study, and none of the FHR patterns identified after the diagnosis of acute chorioamnionitis were significantly associated with infants with pH Ua <7.20. It has been reported that a decreased FHR rate was not associated with intra-amniotic infection in patients subsequently developing cerebral palsy.[23]

In general, gestational stress, such as inflammation, causes the fetus's brain to become sensitive, and a fetus exposed to intra-uterine inflammation may be vulnerable to secondary perinatal injuries, such as hypoxic ischemia, which do not result in significant brain damage.[24] Thus, the conventional method of using the FHR model to determine the presence of hypoxic or fetal acid dose to diagnose intra-uterine inflammation has not been shown to be useful in reducing neurological complications.

Our study shows that an early gestational age, vaginal delivery at the NICU, and an Apgar score of 5 minutes less than 7 are associated with histological CAM.

Factors associated with histological CAM with logistic regression suggest two possible different causes for early histological CAM. The onset of histological CAM at early gestational ages is due to the immaturity of the infection defense mechanism leading to pre-term delivery.

Another possibility is that histological CAM is just one type of inflammation as a result of uterine contractions during labor and delivery. The study has limitations, and the FHR pattern in cases of pre-term delivery less than 28 weeks was not evaluated in this study. Second, only early pre-term fetal complications were assessed and no serious long-term complications such as cerebral palsy and behavioral or learning disorders were assessed. Third, the present study compared FHR patterns recorded 1–2 hours before delivery and is therefore a cross-sectional rather than a longitudinal study. In addition, the present study included cases of normal delivery and cesarean section and did not consider the longitudinal effect of uterine contractions on the FHR pattern. In this study, only the association of HCA in pre-term delivery was investigated.

Therefore, evaluation of long-term complications such as increased cerebral palsy, behavioral disorders, and learning disabilities may be needed in future studies focused on evaluating intra-uterine infection. In the present study, histological CAM diagnosis based on a specific prenatal FHR pattern is difficult. However, an earlier gestational age at delivery was associated with the presence of histological CAM.

These results revealed that not only histological CAM is the cause of pre-term delivery but also the pre-mature outcome and the mode of delivery in early pre-term delivery should be considered in order to reduce the incidence of histological CAM.

Conclusion

This study showed that vaginal delivery, a lower gestational age at delivery at NICU, and an Apgar score of 5 minutes < 7

were associated with an increased risk of histological CAM in cases of pre-term delivery. Also, results in comparison of PROM with HCA and PROM with non-HCA were similar, but the vaginal delivery showed no significant difference in PROM with HCA and PROM with non-HCA. Because the study of fetal injuries is limited to retrospective and cross-sectional research, further prospective and longitudinal studies are needed to evaluate the association between long-term fetal complications and intra-amniotic infection.

Also, due to cost benefit problems, it is suggested that in fetuses with Apgar scores of 5 minutes <7, the need to be admitted to the NICU pathological examination of the placenta for HCA be considered.

Financial support and sponsorship

Isfahan university of medical sciences.

Conflicts of interest

There are no conflicts of interest.

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