

Mahdiyeh Hospital, Tehran, IRAN
The Past, is the light's road of the future!

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Introduction

Chorioamnionitis (CAM) is one of the major risk factors for neonatal early-onset sepsis (EOS). Therefore, different international guidelines were developed by Center for Disease Control (CDC, 2010), Committee on Fetus and Newborn (COFN, 2012), The American College of Obstetrician and Gynecologists (ACOG, 2015) and American Academy of Pediatrics (AAP, 2018) for diagnosis and care of these neonates. This research aimed to evaluate our neonates and then compare with the guidelines. CAM has been reported since 1961. The prevalence of CAM varies based on clinical, microbiological, histological diagnostic criteria from 0.5-10% in normal pregnancies up to 25% in preterm pregnancies. Prevalence of early onset sepsis (EOS) in the late-preterm (LPT) and full-term (FT) neonates born to mothers with CAM were reported 1-3% in those receiving Intra partum Antibiotic Prophylaxis (IAP) and 5-8% without therapy. Diagnosis is the main challenge in CAM. Some studies introduced maternal fever (MF) and some used the criteria of Gibbs et al. Grunberg et al reported that CAM is diagnosed based on MF and one sign by 68.5% only MF by 26.4% and with other symptoms by 4.7% of gynecologists. However, CAM is definitively diagnosed only through histological chorioamnionitis (HCA) assessment, because clinical and microbiological signs have low positive predictive value. Neonatal management is the other challenge! The CDC and COFN recommended lab tests and antibiotic (AB) therapy for all neonates born to mothers with CAM, which faced with widespread oppositions especially for asymptomatic LPT and FT neonates. ACOG recommended using the term Intrauterine Inflammation or Infection or both (Triple I) instead of CAM, and AAP developed guidelines for neonates born at 34 6/7 weeks and 35 0/7 weeks gestational age with EOS to make more accurate decisions for maternal CAM diagnosis, neonatal care for hospitalization, conduction of lab test and administration of antibiotics. The present study aimed to evaluate the provided guidelines and our management of neonates born from mothers with CAM in our center, and also compare the results with other studies.

Methods

All neonates (regardless of the gestational age) born to mothers with CAM (regardless of criteria) were included in this study. In our study, the diagnosis of CAM was based on: clinical suspicion of gynecologist, IPF (T>37.8 °C), maternal leukocytosis (WBC >15000), maternal tachycardia (HR>100/min), fetal tachycardia (FHR>160/min), uterine tenderness, vaginal secretion or foul-smelling amniotic fluid, the Triple I terminology had not been developed yet in the early years of this study. All symptomatic neonates or neonates with EOS signs and symptoms were hospitalized in NICU and received antibiotics after performing the tests. The asymptomatic neonates were observed for 6-12 hours in the NICU, then transferred to the mother's room if they were asymptomatic and tolerate feeding, and if the neonates remained asymptomatic for 24-48 hours, were discharged with their mothers. The diagnosis of EOS was based on blood or cerebrospinal fluid (CSF) culture in the first 3 days after the birth.

Results

From 28,988 live births in our center during the study period, 169 neonates (1.7%) were born to mothers with CAM. The mean gestational age was 35.37±4.04 weeks (30.8% 34w) and the mean birth weight was 2619.35±868.1 g (39% 2500g). Out of 169 neonates under investigation, 99 neonates (58.6%) were asymptomatic, while 47 neonates were observed near mothers, and 7 neonates were hospitalized without antibiotic therapy. Therefore only 45 asymptomatic and 7 symptomatic neonates were hospitalized in NICU and received antibiotics. In 122 hospitalized neonates, CBC (n=122, WBC >24000: 9%), CRP (n=122, Positive: 18%), B/C (n=109, Positive: 2.7%) and LP (n=10, Positive: 10%), more positive in symptomatic neonates. Antibiotics administered to 115 neonates (68%), out of which 45.45% were asymptomatic. Maternal CAM criteria in these neonates were: No MF (n=41/62; 66.1%), Only MF (n=13/19; 68.4%), MF+1 Signs (n=22/37; 59.4%), MF+2 Signs (n=39/51; 76.5%), STI (n=40/53; 75.5%). The duration of antibiotic therapy was <3 days in 58 neonates, 4-7 days in 34 neonates, 8-14 days in 11 neonates, and >14 days in 12 neonates. The hospital course in asymptomatic and symptomatic neonates was 2.59±1.13 vs. 15.15±13.67 days respectively (p<0.001). In total, 7 Symptomatic neonates (34 weeks) with birth weights : 1000 g (n=3), 1001-1500 g (n=2), and 1501-2500 g (n=2), positive blood culture (n=1), CAM criteria: No MF: 4, Only MF : 1, MF+2 signs : 2 ; were died because of Culture Positive EOS (n=1), RDS (n=5), and congenital anomaly (n=1).

Table1. Relationship of Basic Characteristics of Neonates with maternal CAM

Characteristics	Total (n=169)	Total (n=169)		P-Value
		Asymptomatic (n=99)	Symptomatic (n=70)	
Sex				
- Male	85 (50.3%)	48 (49%)	37 (52.9%)	0.58
- Female	84 (49.7%)	51 (51%)	33 (47.1%)	
Birth weight (g)				<0.001
- 1500	24 (14.2%)	0 (0%)	24 (34.3%)	
- 1501-2500	42 (24.8%)	13 (13.1%)	29 (41.4%)	
- >2500	103 (60.9%)	86 (86.9%)	17 (24.3%)	
Gestational Age				<0.001
- <34w	117 (69.2%)	92 (92.9%)	25 (35.7%)	
- 34w	52 (30.8%)	7 (7.1%)	45 (64.3%)	
Type of delivery				0.13
- CS	141 (83.4%)	79 (79.8%)	62 (88.6%)	
- NVD	28 (16.6%)	20 (20.2%)	8 (11.4%)	
Neonate status				<0.001
- Not hospitalized	47 (27.8%)	47 (47.5%)	0 (0%)	
- Asymptomatic	52 (30.2%)	52 (52.5%)	0 (0%)	
- Symptomatic	70 (42.2%)	0 (0%)	70 (100%)	
WBC				0.20
- Abnormal (>24000)	11 (9%)	7 (3.5%)	4 (5.7%)	
- Normal	111 (91%)	45 (66.5%)	66 (94.3%)	
CRP				0.84
- Positive	22 (13%)	5 (6.6%)	17 (24.3%)	
- Negative	100 (82%)	47 (90.4%)	53 (75.7%)	
Blood Culture				0.28
- Positive	3 (2.7%)	0 (0%)	3 (4.3%)	
- Negative	106 (97.3%)	43 (100%)	63 (95.7%)	
LP				1.0
- Abnormal	1 (10%)	0 (0%)	1 (20%)	
- Normal	9 (90%)	5 (100%)	4 (80%)	
Antibiotic in Neonate				<0.001
- Yes	115 (68%)	45 (45%)	70 (100%)	
- No	54 (32%)	54 (55%)	0 (0%)	

Table2. Relationship between Neonates' Characteristics according to the CAM Criteria in symptomatic/ asymptomatic neonates

Characteristics	No Maternal Fever		Maternal Fever Only		Maternal Fever + 1 sign		Maternal Fever + 2 signs		Suspected Triple I	
	Asymptomatic (n=30)	Symptomatic (n=32)	Asymptomatic (n=13)	Symptomatic (n=6)	Asymptomatic (n=24)	Symptomatic (n=13)	Asymptomatic (n=32)	Symptomatic (n=19)	Asymptomatic (n=33)	Symptomatic (n=20)
Sex										
- Male	12 (40%)	18 (56.3%)	8 (61.5%)	2 (33.3%)	10 (41.7%)	6 (46.2%)	18 (56.3%)	11 (57.9%)	19 (57.6%)	11 (55%)
- Female	18 (60%)	14 (43.7%)	5 (38.5%)	4 (66.7%)	14 (58.3%)	7 (53.8%)	14 (43.7%)	8 (42.1%)	14 (42.4%)	9 (45%)
Birth weight										
- 1500	0 (0%)	15 (46.9%)	0 (0%)	1 (16.7%)	0 (0%)	4 (30.8%)	0 (0%)	4 (21.1%)	0 (0%)	5 (25%)
- 1501-2500	4 (13.3%)	10 (31.2%)	2 (15.4%)	4 (66.6%)	4 (16.7%)	6 (46.1%)	3 (9.4%)	9 (47.4%)	3 (9.1%)	9 (45%)
- >2500	26 (86.7%)	7 (21.9%)	11 (84.6%)	1 (16.7%)	20 (83.3%)	3 (23.1%)	29 (90.6%)	6 (31.6%)	30 (90.9%)	6 (30%)
Gestational Age										
- >34w	29 (96.7%)	23 (71.9%)	13 (100%)	1 (16.7%)	21 (87.5%)	7 (53.8%)	29 (90.6%)	8 (42.1%)	30 (90.9%)	8 (40%)
- 34w	1 (3.3%)	9 (22.1%)	0 (0%)	5 (83.3%)	3 (12.5%)	6 (46.1%)	3 (9.4%)	11 (57.9%)	3 (9.1%)	12 (60%)
Neonate status										
- Not hospitalized	15 (50%)	0 (0%)	6 (46.1%)	0 (0%)	14 (58.3%)	0 (0%)	12 (37.5%)	0 (0%)	13 (39.4%)	0 (0%)
- Asymptomatic	15 (50%)	0 (0%)	7 (53.8%)	0 (0%)	10 (41.7%)	0 (0%)	20 (62.5%)	0 (0%)	20 (60.6%)	0 (0%)
- Symptomatic	0 (0%)	32 (100%)	0 (0%)	6 (100%)	0 (0%)	13 (100%)	0 (0%)	19 (100%)	0 (0%)	20 (100%)
WBC										
- Abnormal (>24000)	1 (6.7%)	1 (3.1%)	1 (14.3%)	1 (16.7%)	2 (20%)	0 (0%)	3 (15%)	2 (10.5%)	3 (15%)	2 (10%)
- Normal	14 (93.3%)	31 (96.9%)	6 (85.7%)	5 (83.3%)	8 (80%)	13 (100%)	17 (85%)	17 (89.5%)	17 (85%)	18 (90%)
CRP										
- Positive	1 (6.7%)	7 (21.9%)	3 (42.9%)	4 (66.7%)	0 (0%)	3 (23.1%)	1 (5%)	3 (15.8%)	1 (5%)	3 (15%)
- Negative	14 (93.3%)	25 (78.1%)	4 (57.1%)	2 (33.3%)	10 (100%)	10 (76.9%)	19 (95%)	16 (84.2%)	19 (95%)	17 (85%)
Blood Culture										
- Positive	0 (0%)	1 (3.2%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)	1 (5%)
- Negative	10 (100%)	30 (96.8%)	7 (100%)	5 (83.3%)	9 (100%)	10 (100%)	17 (100%)	18 (94.7%)	17 (100%)	19 (95%)
LP										
- Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
- Normal	1 (100%)	1 (100%)	2 (100%)	2 (100%)	0 (0%)	1 (100%)	2 (100%)	1 (100%)	2 (100%)	0 (0%)
Antibiotic in neonates										
- Yes	9 (30%)	32 (100%)	7 (53.9%)	6 (100%)	9 (37.5%)	13 (100%)	20 (62.5%)	19 (100%)	20 (60.6%)	20 (100%)
- No	21 (70%)	0 (0%)	6 (46.1%)	0 (0%)	15 (62.5%)	0 (0%)	12 (37.5%)	0 (0%)	13 (39.4%)	0 (0%)
Outcome										
- Survive	30 (100%)	28 (87.5%)	13 (100%)	5 (83.3%)	24 (100%)	13 (100%)	32 (100%)	17 (89.5%)	33 (100%)	18 (90%)
- Expire	0 (0%)	4 (12.5%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	2 (10.5%)	0 (0%)	2 (10%)

Table3. Relationship of CAM Criteria in symptomatic/ asymptomatic neonates

Characteristics	Asymptomatic (n=99)	Symptomatic (n=70)	P-Value
Chorioamnionitis (CAM)			
- No Maternal fever	30 (30.3%)	32 (45.7%)	0.22
- Maternal Fever Only	13 (13.1%)	6 (8.6%)	
- Maternal Fever +1 sign	24 (24.3%)	13 (18.6%)	
- Maternal Fever +2 signs	32 (32.3%)	19 (27.1%)	
Suspected Triple I	33 (33.3%)	20 (28.6%)	0.51
Hospital course (day)	2.59±1.13	15.15±13.67	<0.001
Outcome (Death)	0 (0%)	7 (10%)	0.002

Discussion

In this prospective cohort study that was conducted in Mahdiyeh Medical Center, 62 mothers (36.7%) were without IPF: maternal tachycardia (n=13), FHR>160/min (n=2), foul-smelling amniotic fluid (n=1) and clinical suspicion (n=46), in this group 24 neonates were born prior to the 34th week of gestation, 32 neonates were symptomatic, and one neonate's blood culture was positive with E. coli, this group can be regarded as CAM diagnosed by diagnostic criteria other than fever. On the other hand, 19 mothers had only IPF, 37 mothers had IPF with 1 sign, 51 mothers had IPF with 2 signs, and 53 mothers were in the STI group. Therefore totally, 107 mothers had IPF (63.3%). According to the CDC and COFN guidelines, all 169 neonates should be hospitalized, Lab tests done and receive antibiotics; however, we hospitalized only 122 neonates.

According to the ACOG guideline, out of 19 mothers with only IPF (5 neonates born <34th week of gestation and 1 neonate born 34th week of gestation, all symptomatic), therefore 6/19 vs. 13/19 should be hospitalized and treated. Also from 53 mothers with STI (15 neonates born <34th week of gestation and 8 neonates born 34th week of gestation and symptomatic), therefore 23/53 vs. 40/53 should be hospitalized and treated, and totally 29/72 vs. 53/72 should be hospitalized and treated, which indicates a reduction by approximately 50%. In our study, 45/52 of Preterm (PT) <34 weeks neonates (86.5%), 21/32 of Late Preterm (LPT) neonates (65.6%), and 44/85 of Full Term (FT) neonates (51.7%) were hospitalized and treated. Also, the need for hospitalization and antibiotic therapy can be reduced by frequent physical examination of asymptomatic LPT and FT neonates, or using Sepsis Risk Calculator (SRC), and in PT neonates (34 weeks) based on AAP guideline (2018). However, the outcome depends on future clinical studies. Many studies evaluated the sensitivity and specificity of lab tests (CBC, CRP, B/C, LP, etc) but recently AAP(2018) recommend only B/C and CSF/ before antibiotic therapy. In three neonates with positive blood culture, two neonates (2/45, 4.4%) born <34th week of gestation and one neonate (1/64, 1.6%) at 35th week in their mothers was diagnosed based on: No MF (n=1, GA:33 weeks, CRP: Negative, B/C: E. coli), Only MF (n=1, GA:33 weeks, CRP: Positive, B/C: Staph Epidermidis), MF+2 signs (n=1, GA=35 weeks, CRP: Positive, B/C and CSF/C: Acinetobacter). All three neonates were symptomatic at birth. However the culture negative sepsis (CNS) continues to remain a "medical myth" and it is very important to distinguish between asymptomatic neonates born to mothers with CAM from asymptomatic neonates with EOS. In the present study, the hospital course of stay was 2.02±0.62 days for asymptomatic neonates without antibiotic therapy, 3.21±1.23 days for asymptomatic neonates with antibiotic therapy, and 15.15±13.67 days for symptomatic neonates with antibiotic therapy.

Conclusion

Our study showed that, Similar to other studies against CDC and COFN, more than 50% of our neonates born >34th week of gestation did not receive antibiotics, also had short hospital course, antibiotic day, low EOS. Our study revealed that at present time ACOG guidelines are effective in reducing hospitalization of neonates born 34th week of gestation and for neonates <34 6/7 weeks' of gestation AAP guideline (2018) should be considered in future clinical trials. The combination of guidelines (ACOG & AAP) may reduce the hospitalization, Laboratory tests, antibiotic prescription, and other complications.