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Does the Degree of Maternal Fever in the Setting of Chorioamnionitis Lead to Adverse Neonatal Outcomes?

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Abstract

Objective The effect of the degree of maternal fever in the setting of chorioamnionitis on neonatal morbidity is unclear. The objective of this study is to assess the association between high maternal fevers ($\geq$ 39°C) on neonatal morbidity.

Study Design Secondary analysis of Maternal-Fetal Medicine Units (MFMU) Cesarean Registry data obtained from 1999 to 2002 among singleton gestations with chorioamnionitis. Women with a temperature less than 39°C (low fever) compared with those with greater than or equal to 39°C (high fever). Primary outcome was a composite of adverse neonatal outcomes such as death, sepsis, necrotizing enterocolitis, grade-3 or -4 intraventricular hemorrhage, seizure within 24 hours of delivery, intubation within 24 hours of delivery, and requiring cardiopulmonary resuscitation. Demographic characteristics compared using Fisher's exact and Wilcoxon's rank-sum test as appropriate. Multivariate logistic regression analysis with performed to control for cofounders. Stratified analysis also performed to assess outcomes in term infants.

Results Of 1,313 included women, 1,200 (91.3%) were in the low fever group and 113 (8.7%) were in the high fever group. Women in the high fever group were more likely to be African American and group B *Streptococcus* positive. No difference in primary outcome was noted between the groups (38.9% high fever vs. 35.8% low fever, $p = 0.54$). High maternal fever was associated with increased risk of NICU admission (48.1 vs. 50.4%, $p = 0.02$). When controlling for African American race, preterm birth, and delivery route, patients with high fever were not more likely to have adverse neonatal outcomes (adjusted odds ratio [aOR] = 1.28, 95% confidence interval [CI]: 0.84, 1.98). In the analysis limited to term infants, when controlling for confounders, high fever, similarly, was not associated with increased odds of adverse neonatal outcomes (aOR = 1.59, 95% CI: 0.96, 2.65).

Conclusion The degree of maternal fever does not appear to be associated with an increased likelihood of adverse neonatal outcomes. Better understanding maternal factors that affect neonatal morbidity in the setting of chorioamnionitis is critical.

Keywords
- chorioamnionitis
- intra-amniotic infection
- neonatal outcome
- maternal fever

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Key Points

- High maternal fever in the setting of chorioamnionitis does not appear to have an increased likelihood of adverse neonatal outcomes.
- It is important to identify factors that may increase the risk of adverse outcomes such as early onset sepsis.
- Maternal fever may not be a strong indicator for neonatal outcomes and antibiotic protocols.

Chorioamnionitis, also known as intra-amniotic infection (IAI), occurs in approximately 1 to 4% of all births in the United States and is associated with serious maternal and perinatal adverse outcomes. Approximately 12 to 13% of cesarean deliveries are affected by chorioamnionitis.[1] IAI is typically caused by ascending polymicrobial bacterial infection in the setting of rupture of membranes; however, it can occur in the setting of intact amniotic membranes, although this is far-less common.[2] Chorioamnionitis is caused by multiple microorganisms, often including the genital mycoplasmas *Ureaplasma urealyticum* and *Mycoplasma hominis*.[3] Other organisms associated with chorioamnionitis include *Gardnerella vaginalis*, group B *Streptococcus*, and *Escherichia coli* which are commonly part of vaginal and enteric flora, respectively.[3–7]

Chorioamnionitis has been shown to increase risk of adverse maternal outcomes such as cesarean delivery, postpartum hemorrhage, endometritis, and wound infection. In rare instances, patients can develop sepsis, adult respiratory distress syndrome, and ultimately death.[7,8] Adverse fetal outcomes associated with chorioamnionitis include fetal death, neonatal sepsis, intraventricular hemorrhage (IVH), cerebral white matter damage, and long-term disability.[9] Preterm infants are at higher risk of these complications than term infants.[9,10] Clinical findings of intrauterine amniotic infection include maternal fever, fetal tachycardia ($>$ 160 beats per minute), uterine fundal tenderness, and purulent or foul-smelling amniotic fluid. Although low-grade fever can be transient in labor, maternal fever greater than 100.4°F warrants further evaluation.[11,12] Additionally, we know that maternal IAI negatively impacts neonatal outcomes, particularly in term infants.

In most instances, the presence of maternal fever and at least one other sign, in the absence of other etiologies, is required to make a diagnosis of clinical chorioamnionitis.[12,13] Previous older definitions included maternal tachycardia which has since been dropped from the definition of IAI.[13] Isolated maternal fever has been shown to have adverse neonatal outcomes, as well as including lower 1-minute Apgar's scores, and neonatal oxygen requirement; this effect is more prevalent with higher degree of fever.[14] A better understanding of the relationship between these clinical findings in the setting of chorioamnionitis on adverse maternal and neonatal outcomes is needed to better counsel patients on maternal and neonatal risks. The objective of this study was to assess the impact of high maternal fever ($\geq$ 39°C) in the setting of chorioamnionitis on neonatal morbidity.

Materials and Methods

We performed a secondary analysis of the Maternal-Fetal Medicine Units (MFMU) Cesarean Registry.[15] The original MFMU Cesarean Registry was created with the primary purpose of evaluating factors that influence the likelihood of a successful vaginal birth after cesarean (VBAC) after 1 prior cesarean section. Inclusion criteria for this large multicenter prospective observational study included women with one prior cesarean with term-singleton pregnancies (known low transverse scar or unknown scar) undergoing trial of labor.

Inclusion criteria for this analysis include women with a diagnosis of chorioamnionitis, (as defined by the original study as: clinical diagnosis of chorioamnionitis with an elevated body temperature). Presence of maternal and fetal tachycardia, uterine tenderness, and malodorous fluid were collected; however, these variables were not released with the deidentified dataset. The diagnosis of chorioamnionitis was made clinically by the provider. Exclusion criteria include multiple gestations, stillbirths, and patients with missing infection or delivery data. The MFMU Cesarean Registry dataset was built by trained study nurses who reviewed all available medical records of 14,529 women from 19 academic centers. Data regarding demographics, obstetric and medical history, and intrapartum events was collected from 1999 to 2002. Receipt of prenatal care was

Table 1 Maternal demographics

Characteristics	Maternal temperature 39 °C $n = 1{,}200$ (%)	Maternal temperature $\geq$ 39 °C $n = 113$ (%)	*p*-Value
Maternal age (y) Median (IQR)	29 (23, 33)	28 (23, 32)	0.36
No prenatal care	68 (5.7)	2 (2.9)	0.08
African American Race	409 (34.1)	54 (47.8)	$<$ 0.01
Public insurance	614 (51.2)	60 (53.1)	0.77
Prior vaginal delivery	382 (32.2)	31 (27.7)	0.34
Pregnancy history of pyelonephritis	17 (4.3)	3 (7.1)	0.43
Pregnancy history of urinary tract infection	151 (38.0)	17 (40.5)	0.74
Pregnancy history of vaginal infection	184 (15.3)	19 (16.8)	0.68
Maternal chronic hypertension	22 (1.8)	2 (1.8)	$>$ 0.99
Maternal diabetes	96 (8.0)	7 (6.2)	0.59
Substance use			
Tobacco	162 (13.5)	12 (10.6)	0.47
Alcohol	49 (4.1)	3 (2.7)	0.62
Drugs	69 (5.8)	2 (1.8)	0.81

Abbreviation: IQR, interquartile range.

defined by the original study as having two or more prenatal visits, not including visits to the emergency room. This study was considered exempt from the Institutional Review Board (IRB; identifier no.: Pro00057547).

Statistical Analysis

Chorioamnionitis was clinically identified and maximum maternal temperature was then defined as the exposure of interest. Women with maximum maternal temperature of less than 39°C (low maternal temperature) are classified as controls. Cases were defined as women with maximum maternal temperature greater than or equal to 39°C (high maternal temperature; ►**Table 2**). Demographic characteristics compared using Fisher's exact and Wilcoxon's rank-sum test as appropriate. The primary outcome was an adverse neonatal composite score composed of death, confirmed/presumed neonatal sepsis, necrotizing enterocolitis, grade-3 or -4 intraventricular hemorrhage (IVH), neonatal seizure, neonatal intubation within 24 hours, and need for neonatal cardiopulmonary resuscitation (CPR). Secondary outcomes included neonatal intensive care unit (NICU) admission, median NICU length of stay, neonatal respiratory distress, and delivery arterial cord gas less than 7.10 (►**Table 3**).

Multivariate logistic regression was performed to adjust for potential confounding factors using backward stepwise regression with variables with *p*-value less than 0.2, remaining in the final model to predict factors associated successful VBAC. Confounding variables in this model included body mass index, gestational age, fetal sex, African American race, oxytocin use, operative delivery, labor length, and antibiotic administration. A second planned regression was performed, stratifying patients into term and preterm deliveries. Confounding variables in these models included maternal body mass index (BMI) at delivery, fetal sex, African American race, oxytocin use, operative delivery, antibiotic administration and labor length. *p*-Values and adjusted odds ratios (aORs) are reported. Analyses were performed using Stata software (Version 14.0; Stata Corporation LLC, College Station, TX).

Results

Of the 14,529 women included in the original MFMU Cesarean Registry Study, 1,313 women met inclusion criteria. In the study cohort, 1,200 (91.4%) women with chorioamnionitis had maternal temperature less than 39°C (low fever)

Table 2 Labor and delivery characteristics

Characteristic	Maternal temperature $< 39\,^{\circ}C$ $n = 1{,}200$ *n* (%)/median (IQR)	Maternal temperature $\geq 39\,^{\circ}C$ $n = 113$ *n* (%)/median (IQR)	*p*-Value
Median gestational age at delivery (wk)	39 (32.7, 40.3)	39.2 (36.1, 40.3)	0.51
BMI at delivery	32.0 (28.6, 36.4)	31.6 (27.7, 36.4)	0.29
Preterm birth (< 37 wk)	402 (33.5)	31 (27.3)	0.21
Fetal congenital anomaly	37 (3.1)	3 (2.7)	> 0.99
Pregnancy related hypertension	54 (4.5)	9 (8.0)	0.11
Median admission white blood cell count ($\times 10^9$/L)	11.6 (9.4, 15.1)	11 (9, 14.1)	0.19
Male fetus	608 (50.7)	67 (59.3)	0.09
Median duration of labor (h)	13.4 (7.9, 22.1)	14.2 (7.4, 24)	0.67
Median duration of ruptured membranes (h)	11.3 (6.7, 20.6)	10.1 (6.7, 18.5)	0.29
Use of Foley's balloon ripening	27 (2.3)	2 (1.8)	> 0.99
Labor/IOL	1,077 (89.8)	102 (90.3)	> 0.99
Oxytocin	626 (52.2)	68 (60.2)	0.12
Epidural use	871 (75.7)	87 (80.6)	0.29
GBS positive (treated)	227 (19.7)	9 (8.3)	0.003
Exposed to intrapartum Abx	1,098 (91.5)	103 (91.2)	0.86
Ampicillin and gentamicin	431 (35.9)	43 (38.1)	0.687
Clindamycin and gentamicin or cephalosporin/gentamicin	370 (30.8)	37 (32.7)	
Partial or other regimen	399 (33.3)	33 (32.9)	
Meconium stained fluid	263 (21.9)	32 (28.3)	0.13
Operative vaginal delivery	103 (8.6)	12 (12.4)	0.17
Cesarean	685 (57.1)	60 (53.1)	0.43

Abbreviations: Abx, antibiotics; BMI, body mass index; GBS, group B *Streptococcus*; IOL, induction of labour; IQR, interquartile range.

Table 3 Adverse neonatal outcomes

Characteristic	Maternal temperature $< 39\,^{\circ}C$ $n = 1{,}200$ n (%)/median (IQR)	Maternal temperature $\geq 39\,^{\circ}C$ $n = 113$ n (%)/median (IQR)	p-Value
Neonatal composite	429 (35.8)	44 (38.9)	0.54
Death	52 (4.5)	3 (2.9)	0.62
Confirmed or presumed sepsis	399 (33.3)	42 (37.2)	0.41
Necrotizing enterocolitis	28 (2.3)	3 (2.7)	0.75
Grade-3 or -4 IVH	31 (2.6)	1 (0.9)	0.52
Seizure with 24 hours	23 (2.0)	2 (1.9)	1.00
Required intubation within 24 hours	25 (2.1)	3 (2.7)	0.73
Required CPR	25 (2.1)	3 (2.7)	0.73
Secondary outcomes			
NICU admission	577 (48.1)	57 (50.4)	0.69
Median NICU LOS (d)	10 (4, 32)	7 (4,20)	0.09
Respiratory distress	249 (20.8)	19 (16.8)	0.39
Cord gas < 7.10	32 (2.7)	7 (6.2)	0.07

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; IVH, intraventricular hemorrhage; LOS, length of stay; NICU, neonatal intensive care unit.

and 113 (8.6%) had a maternal temperature greater than or equal to 39°C (high fever).

Women with low fever were more likely to be of African American race (34.1 vs. 47.8%, $p < 0.01$). No other significant differences were noted between the groups (►**Table 1**). Additionally, no significant differences were noted in mean gestational age at delivery (39 vs. 39.2 weeks, $p = 0.51$), maternal BMI at delivery (32.0 vs. 31.9 weeks, $p = 0.29$), or preterm delivery (33.5 vs. 27.3%, $p = 0.21$). The length of labor (13.4 vs. 14.2 h, $p = 0.67$) or rupture of membranes (11.3 vs. 10.1, $p = 0.29$) was not significantly different either.

A total of 429 (35.8%) of women with low fever and 44 (38.9%) with high fever had adverse neonatal outcome, as previously defined, ($p = 0.54$). Similarly, no significant differences in the individual composite components were noted, (►**Table 3**). After stratifying by term and preterm gestational age, no significant differences were seen in the adverse neonatal outcomes for term infants (23.6 vs. 30.2%, $p = 0.19$) or in preterm infants (66.7 vs. 66.7%, $p > 0.99$) deliveries. However, among term deliveries, a significantly higher rate of NICU admission occurred in women with high fevers (33.0 vs. 45.4%, $p = 0.02$). In term deliveries, 8 infants had confirmed sepsis and 188 had presumed sepsis out of 196 infants in the primary composite. In preterm deliveries, the opposite was true, women with high fevers had a significantly lower NICU admission rate (86.7 vs. 66.7, $p = 0.01$; ►**Table 4**).

When controlling for confounders, high fever was not associated with a significant difference in neonatal outcomes

Table 4 Adverse neonatal outcome: stratified gestational age by term and preterm

Characteristic	Women with chorioamnionitis n (%)/median (IQR)		p-Value
	Maternal temperature $< 39\,^{\circ}C$	Maternal temperature $\geq 39\,^{\circ}C$	
Gestational age ≥ 37 weeks ($n = 947$)			
Primary outcome			
	$n = 798$	$n = 82$	
Composite	203 (23.6)	26 (30.2)	0.19
Death	2 (0.23)	0	> 0.99
Confirmed or presumed sepsis	171 (21.4)	25 (30.5)	0.23
Secondary outcome			
NICU admission	284 (33.0)	39 (45.4)	0.02
Median NICU LOS (d)	5 (4,8)	5 (4,8)	0.81
Cord gas < 7.10	29 (3.4)	5 (5.8)	0.23
Gestational age < 37 weeks ($n = 433$)			
Primary outcome			
	$n = 402$	$n = 31$	
Composite score	226 (66.7)	18 (66.7)	> 0.99
Death	50 (16.8)	3 (15.8)	> 0.99
Confirmed or presumed sepsis	200 (59.0)	17 (63.0)	0.84
Secondary outcomes			
NICU admission	293 (86.4)	18 (66.7)	0.01
Median NICU LOS (d)	35 (18, 74)	54 (22, 111)	0.12
Cord gas < 7.10	3 (0.88)	2 (7.41)	0.05

Abbreviations: IQR, interquartile range; LOS, length of stay; NICU, neonatal intensive care unit.

(aOR = 1.26; 95% confidence interval [CI]: 0.78, 2.02). In the analysis stratified by gestational age at delivery, high fever was not associated with adverse neonatal outcomes in term or in preterm deliveries (aOR = 1.59, 95% CI: 0.96, 2.65; ►**Table 5**).

Discussion

In this study, maternal temperature greater than or equal to 39°C was not associated with adverse neonatal outcomes in the setting of chorioamnionitis, even when stratifying by gestational age at delivery. However, in term infants with IAI, higher maternal fever was associated with higher rates of NICU admission.

It is clear that chorioamnionitis is a significant risk factor for early-onset sepsis (EOS). What aspects of the IAI impact that risk are less well-defined. Other authors have studied the impact of maternal fever to be a significant risk factor for

Table 5 Unadjusted and adjusted analysis of association of maternal temperature $\geq$ 39 with adverse neonatal outcomes for infants by gestational age at delivery

	OR (95% CI)	aOR (95% CI)
All comers	1.15 (0.77, 1.7)	1.28 (0.84, 1.98)[a]
$\geq$ 37 weeks	1.65 (1.01, 2.71)	1.59 (0.96, 2.65)[b]
$<$ 37 weeks' EGA	0.81 (0.38–1.69)	0.88 (0.41, 1.85)[b]

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; EGA, estimated gestational age; OR, odds ratio.
Note: Final *n* for each multivariable model as follows: $<$ 37 weeks ($n = 433$) and $\geq$ 37 weeks ($n = 880$).
[a]Controlled for maternal body mass index (BMI) at delivery, gestational age, fetal sex, African American race, oxytocin use, operative delivery, antibiotic administration, labor length.
[b]Controlled for maternal BMI at delivery, fetal sex, African American race, oxytocin use, operative delivery, antibiotic administration, and labor length.

neonatal sepsis.[16] In a nested case-control study of 340 women delivering at more than or equal to 34 weeks, Puopolo et al found a linear relationship between degree of fever and risk of EOS. This study also found longer duration of membrane rupture to be associated linearly with risk of EOS. Due to low numbers of confirmed EOS in our study, the primary outcome is focused on a composite of adverse neonatal outcomes, and not EOS alone, which might explain the difference in the results.

Empiric treatment of neonates born to women with IAI has been routinely recommended in treatment algorithms from the American Association of Pediatrics, the Center for Disease Control and Prevention, and the National Institute for Health and Care Excellence.[17,18] However, more recently, in an attempt to limit use of empiric antibiotics, another recent guideline differentiates neonatal treatment recommendations based on clinical neonatal appearance and isolated fever versus suspected or confirmed IAI.[19] A new risk-based approach was recently developed by Kaiser Permanente, using multivariable prediction models, to estimate the risk of EOS and provide suggested treatment algorithms. This model includes degree of maternal fever, time of ruptured membranes, and antibiotic administration.[20] Comparison of treatment algorithms based on the National Institute for Health and Care Excellence (NICE) guidelines for empiric treatment versus risk-based treatment guided by the Kaiser sepsis risk calculator found a relative reduction in empiric antibiotic use of 74% without missed cases of EOS.[21] Towers et al calculated the rate of intrapartum fever ($>$ 38 °C) at approximately 6.8% and the number needed to treat as 412.[22] As the Kaiser sepsis risk calculator uses maternal fever as a variable in risk assessment, further study is needed to better understand the relationship between high maternal fever and neonatal outcomes, beyond the very rare outcome of confirmed EOS.

Strengths and Limitations

Our study has notable strengths. It is one of the first to evaluate whether maternal fever is an independent risk factor for neonatal outcomes. We were able to control for many cofounders as data were collected by a trained research team and provides good accuracy and consistency to our secondary analysis. The administration and type of antibiotic administered for treatment of chorioamnionitis was also evaluated in our secondary analysis. This variable is crucial, as it has been previously shown to be an important component of multivariate risk assessment models for early onset neonatal sepsis.[16,20]

Our study also has several limitations. The secondary analysis was performed on women undergoing TOLAC which may not be generalizable to a larger population. The definition of chorioamnionitis used by the MFMU Cesarean Registry was based on clinical diagnosis, not using the new IAI definition given the timeframe of the study.[13] Additionally, we were limited by the lack of released data regarding the diagnostic criteria. Thus, some women diagnosed with chorioamnionitis in the study may not meet the current IAI definition.[13] With the current definition of IAI, some of our control group could have been classified as isolated maternal fever if the risk factor for chorioamnionitis was initially maternal tachycardia. Additionally, there is not a diagnostic confirmation of chorioamnionitis by either amniotic fluid culture or gram stain and/or placental pathology, though this is not something routinely used in clinical management. The type of antibiotic was collected in the Cesarean Registry, but we were not able to control for duration of therapy in the current study.

Conclusion

Identifying risk factors for adverse neonatal outcomes can provide additional information to guide postnatal assessment and treatment. Our study sought to evaluate the independent effect of degree of maternal fever. Interestingly, prior studies have shown increased degree of maternal fever to be a significant risk factor for neonatal sepsis. However, in our study, the degree of maternal fever was not significantly associated with adverse neonatal outcome or sepsis alone. Reevaluating the impact of IAI and adverse neonatal outcomes may prove to be different as definitions have changed. Further studies to better identify and confirm true risk factors for adverse neonatal outcomes will better help guide neonatal management and treatment.

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Conflict of Interest
None declared.

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