Original Article

The Role of Intrapartum Fever in Identifying Asymptomatic Term Neonates With Early-Onset Neonatal Sepsis

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OBJECTIVE:
To assess the role of intrapartum fever in identifying asymptomatic term neonates with early-onset neonatal sepsis.

STUDY DESIGN:
Retrospective review of all term neonates with sepsis over a 7-year period to evaluate the significance of symptoms at delivery and intrapartum sepsis risks factors in identifying neonates with sepsis.

RESULTS:
Fifty-three of 90 term neonates with sepsis (59%) were asymptomatic at delivery. Thirty-five of 53 asymptomatic term neonates (66%) met criteria for sepsis evaluations and 18 (34%) were evaluated when symptoms developed after delivery. Among the 35 asymptomatic term neonates meeting criteria for sepsis evaluations, 14 (40%) had evaluations because of intrapartum fever. Thus, 14 of 53 (26%) asymptomatic term neonates with sepsis (30% of GBS sepsis and 11% of non-GBS sepsis) would not have been evaluated if intrapartum fever were ignored.

CONCLUSION:
Over half of term neonates with sepsis were asymptomatic at delivery. Intrapartum fever was helpful in identifying over a quarter of asymptomatic term neonates with sepsis.
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INTRODUCTION

Neonatal sepsis is rare in term neonates with an uneventful labor and delivery with reported rates of 0.8 to 1.2 per 1000 births.[1,2] Nevertheless, studies indicate that a relatively high proportion of term neonates is evaluated for sepsis. One study showed that 15% of neonates greater than 2000 g had a sepsis evaluation when less than 1% actually had blood culture–confirmed sepsis.[3] Another study showed that 25% of term neonates underwent sepsis evaluations with less than 1% with documented sepsis.[4] As neonatal sepsis is considered a ''low incidence, high risk of mortality'' disease, it has been acceptable practice to evaluate and treat many more neonates for this condition than actually those who have the disease.[5]

General agreement exists that all symptomatic neonates should undergo sepsis evaluations and early treatment.[5,6] Group B *Streptococcus* (GBS) has been the leading cause of early-onset neonatal sepsis (EONS)[1] and term neonates with GBS EONS have been reported to present with symptoms of sepsis in the first 24 hours of life.[7] *Escherichia coli* is the second leading cause of EONS.[8] Neonatal symptoms in term neonates with *E. coli* or non-GBS EONS have not been well described. Despite the appearance of symptoms of sepsis within the first 24 hours of life in term neonates with GBS EONS, delaying treatment until symptoms develop may bring the risk of preventable morbidity and mortality.[5]

Neonatologists have used intrapartum maternal risk factors such as fever, prolonged rupture of membranes, and chorioamnionitis to determine if asymptomatic neonates should undergo a neonatal sepsis evaluation right after delivery. However, whereas these risk factors may signify maternal infection that could affect the neonate, recent research indicates that for women with term pregnancies, much of intrapartum fever may actually be a consequence of epidural analgesia.[4] As differentiating between intrapartum fevers related to infections or related to use of epidural analgesia is not clinically possible currently, many term neonates without sepsis undergo sepsis evaluations. It is not known whether the presence of intrapartum risk factors such as fever is helpful in identifying those asymptomatic term neonates with EONS in a population with a high rate of epidural analgesia usage.

We conducted this study to examine the clinical presentation of term neonates with blood culture–confirmed EONS, especially among neonates with GBS EONS compared to neonates with non-GBS EONS. We were particularly interested in the proportion of term neonates with EONS who were asymptomatic at delivery and to determine if intrapartum fever was helpful in identifying those neonates.

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METHODS

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

We identified all term neonates with EONS at Brigham and Women's Hospital between 1990 and 1996. Brigham and Women's Hospital is a tertiary care referral center with over 9000 deliveries per year. We further categorized term neonates with EONS into ones with GBS EONS and non-GBS EONS. A neonate was considered to have EONS if a positive blood culture within the first 7 days of life was found, a diagnosis of sepsis was made by the neonatologists, and appropriate antibiotic therapy for EONS was given. Neonates with positive blood cultures within the first 7 days of life were identified in the following manner. A list of all neonates born in the 7-year study period with their corresponding medical record numbers, birthdates, and birthtimes was generated from the hospital database. This list was then compared to the microbiology laboratory list of all hospital patients with positive blood cultures in the same 7-year study period plus 7 days. Information from the microbiology list included the medical record number, date and time of culture, and organism cultured. A medical record review was performed on those neonates whose medical record numbers were on both lists and whose positive blood cultures were drawn within 7 days of life to ascertain gestational age at delivery, diagnosis of sepsis by neonatologists, and antibiotic administration to neonates. Neonates who were born before 37 weeks of completed gestation were excluded from the current analysis. Neonates with organisms isolated from the blood culture, which were considered skin flora contaminants by the neonatologists, were also excluded from the study. Antibiotic receipt of at least 7 days was considered appropriate therapy for a case of EONS. Antibiotic receipt of less than 7 days was considered appropriate therapy for a neonate with EONS if the neonate expired or was transferred to another hospital on treatment before 7 days of life.

We then identified those term neonates with EONS who had symptoms suggestive of infection at delivery and after delivery by noting presence or absence and timing of symptoms. Symptoms noted at delivery included poor effort, tachypnea, respiratory distress, grunting/flaring/retracting, and hypotonia. Each symptom was coded as transitional or not. Nontransitional symptoms included those symptoms persisting for greater than 15 minutes despite usual delivery room care. Term neonates who were symptomatic at delivery were defined as neonates with nontransitional symptoms. Symptoms noted after delivery included poor respiratory effort, tachypnea, respiratory distress, grunting/flaring/retracting, temperature instability, jitteriness, seizures, hypoglycemia, and poor feeding.

At the time of the study, all neonates with symptoms suggestive of infection at delivery or after delivery would undergo a neonatal sepsis evaluation. The decision to perform a sepsis evaluation on asymptomatic neonates was based on standardized criteria developed by the Joint Program in Neonatology of Harvard Medical School. Neonatal sepsis evaluation at our institution consisted of a blood culture and a complete blood count of the neonate.

We next identified those term neonates with EONS who were asymptomatic but met criteria for sepsis evaluation. At the time of the study, sepsis evaluations were performed in the presence of one major or two minor criteria prior to and at delivery. Major criteria included a maternal temperature >100.4 °F, rupture of membranes for >24 hours, or a sustained fetal heart rate of >160 beats/min. Minor criteria included a low-grade maternal temperature >99.5 °F, rupture of membranes >12 hours, maternal admission white blood cell count of >15,000 cells/ml, or an Apgar score of <7 at 5 minutes. Maternal GBS status was not routinely evaluated at the time of this study.

Finally, we documented the use of intrapartum antibiotics by noting type of antibiotic, timing of administration, number of doses, and indication for antibiotic administration. We also evaluated the neonatal outcomes as determined by birth weight and length of hospitalization at Brigham and Women's Hospital and disposition (home, transfer to another hospital, or death). We also calculated a mortality rate for term neonates with EONS.

Statistical analysis included χ-squared analysis and Fisher exact tests when the expected frequencies were less than five in any cell. A p value of less than 0.05 was considered to represent a statistically significant difference.

RESULTS

Identification of Population With EONS

From 1990 to 1996, 56,838 neonates were delivered at term. Ninety term neonates with blood culture–confirmed EONS were identified for a rate of 1.6 cases per 1000 live term births. Sixty-five term neonates (72%) had GBS EONS and 25 term neonates (28%) had non-GBS EONS. The rates of EONS caused by GBS and non-GBS organisms were 1.1 and 0.4 per 1000 live term births, respectively. The frequency of organisms identified is shown in Table 1.

Eighty-nine of the 90 neonates had their positive blood culture within 72 hours of life. One neonate had a positive blood culture on day 6 of life. The organism identified in that case was *Flavimonas oryzihabitans*.

Table 1 Organisms Isolated From Blood Cultures of Term Neonates With EONS at the Brigham and Women's Hospital from 1990 to 1996

Organism	*n*	%
GBS	65	72.2
E. coli	6	6.7
Staphylococcus aureus	6	6.7
Viridans streptococci	3	3.3
Enterococcus species	2	2.2
Coagulase-negative staphylococci	2	2.2
Streptococcus bovis	2	2.2
Others*	4	4.5

*One each of the following organisms: *Actinomyces* species, *Bacteriodes* species, *Flavimonas* species, and *Str. pneumoniae.*

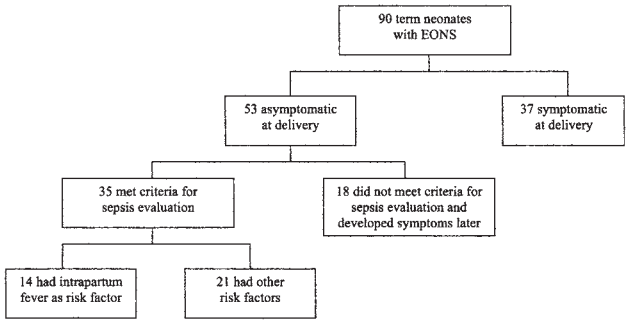

Figure 1. Term neonates with EONS according to symptoms at delivery and criteria for sepsis evaluation.

The neonates were all greater than 2500 g at birth except for two neonates at 2060 and 2300 g, respectively. The mean was 3439 g with a range of 2060 to 4810 g.

Of the 90 term neonates with EONS, 53 (59%) were asymptomatic at delivery and 37 (41%) were symptomatic at delivery. Figure 1 depicts the distribution of the 90 term neonates with EONS according to symptoms at delivery and criteria for sepsis evaluation. Of the 53 asymptomatic term neonates, 44 (83%) had GBS EONS and 9 (17%) had non-GBS EONS. Of the 37 symptomatic term neonates, 21 (57%) had GBS EONS and 16 (43%) had non-GBS EONS. Term neonates with GBS EONS were 1.5 times more likely (95% CI 1.1–2.0; $p=0.006$) to be asymptomatic at delivery than term neonates with non-GBS EONS (68% GBS, 26% non-GBS).

Asymptomatic Term Neonates With EONS

In the 53 asymptomatic term neonates with EONS, 35 (66%) met criteria for sepsis evaluations either because of one major intrapartum risk factor for EONS or two minor intrapartum risk factors. The remaining 18 (34%) asymptomatic term neonates had no intrapartum risk factors and were evaluated when symptoms developed after delivery. Of the 18 asymptomatic term infants who developed symptoms after delivery, 15 (83%) developed symptoms within 24 hours of life.

The percentage of asymptomatic term neonates with GBS EONS who met criteria for sepsis evaluations was not different from neonates with non-GBS EONS (68% compared to 56%, $p=0.5$). In the 44 asymptomatic term neonates with GBS EONS, 30 (68%) met criteria for sepsis evaluations. The remaining 14 (32%) asymptomatic term neonates with GBS EONS had no intrapartum risk factors and were evaluated when symptoms developed after delivery (11 [79%] developing symptoms within 24 hours of life). In the nine asymptomatic term neonates with non-GBS EONS, five (56%) met criteria for neonatal sepsis and the remaining four (44%) were evaluated when symptoms developed after delivery within 24 hours of life.

Table 2 depicts intrapartum sepsis risk factors in asymptomatic term neonates with EONS. We specifically evaluated the impact of intrapartum fever (maternal temperature >100.4 °F) in identifying asymptomatic term neonates with EONS. If intrapartum fever were not included as a sepsis risk factor that would prompt a sepsis evaluation, 14 of 53 (26%) asymptomatic term neonates with EONS would not have been evaluated. With regards to the 44 asymptomatic term infants with GBS EONS, 13 (30%) would not have been evaluated. With respected to the nine asymptomatic term neonates with non-GBS EONS, one (11%) would not have been evaluated.

Use of Intrapartum Antibiotics

In this population of term neonates with EONS, the use of intrapartum antibiotics did not significantly differ in the mothers of term neonates with EONS who were asymptomatic at delivery compared to those who were symptomatic at delivery (13% compared to 16%, $p=0.7$).

Outcomes of Term Neonates With EONS

Seventy-seven (86%) term neonates with EONS were discharged to home with a mean length of hospitalization of 12 days (SD 7.2). Twelve (13%) were discharged to a community hospital or a level 3 neonatal intensive care unit. The only case of mortality (1% mortality rate in term neonates with EONS) was in a neonate with multiple congenital anomalies with an abnormal karyotype who was asymptomatic at delivery but developed symptoms at 3 hours of life with a negative sepsis work-up and then recurrence of symptoms on day 3 of life with a blood culture positive for *E. coli*.

We then compared different groups to see if there were differences in the discharge to home rate. There was no significant difference in the percentage of asymptomatic term neonates who went home compared to symptomatic term neonates (87% vs 84%, $p=0.7$). Similarly, there was no difference in the percentage of term neonates with GBS EONS who went home compared to term neonates with

Table 2 Intrapartum Sepsis Risk Factors in Asymptomatic Term Neonates With EONS

Organism in blood culture	*n*	Intrapartum sepsis risk factors			
		Temperature >100.4 °F only	Temperature between 99.5 and 100.4 °F as a minor criterion	Other criteria	None
GBS	44	13	4	13	14
Non-GBS	9	1	1	3	4
Total	53	14	5	16	18

non-GBS EONS (85% vs 88%, $p = 0.7$). In addition, there was no difference in the percentage of asymptomatic term neonates who went home and had sepsis evaluations because of intrapartum risk factors compared to those who had evaluations when symptoms developed later (91% vs 78%, $p = 0.2$).

DISCUSSION

Management of symptomatic term neonates is not controversial as all need evaluation for infection and early treatment.[5,6] In our study, more than half of term neonates with EONS were asymptomatic at delivery. Two-thirds was evaluated because of intrapartum sepsis risk factors and the remaining third received sepsis evaluations when symptoms suggestive of infection developed after delivery. This confirms that one cannot rely on symptoms at delivery alone to identify neonates with possible sepsis but must note intrapartum sepsis risk factors. The question is which sepsis risk factors to take into account and whether they should be weighted.

When chorioamnionitis is present, the risk of proven sepsis increases to 3% to 5%.[5] The clinical diagnosis of chorioamnionitis is often difficult to confirm, but may be suspected in the presence of maternal intrapartum fever, especially in patients with preterm pregnancies. However, studies have documented that use of epidural analgesia for pain relief during labor is associated with increases in maternal temperatures in patients with term pregnancies.[9–11] Two studies demonstrated that in term populations, over 95% of intrapartum fever occurred in women receiving epidural analgesia.[4,12] Furthermore, two studies have shown an increase in sepsis evaluations in term neonates born to those women with epidural-related fever.[4,13] This results in a dramatic decrease in specificity and positive predictive value of intrapartum fever as a risk factor for sepsis. One question is whether or not one can ignore the presence of intrapartum fever as a sepsis risk factor in term neonates. In our study, we found that 26% of asymptomatic term neonates with EONS (30% of neonates with GBS EONS and 11% of neonates with non-GBS EONS) would not have been evaluated for sepsis if intrapartum fever were not taken into consideration. Almost all of these infants would have developed symptoms suggestive of infection at some time after delivery and would have then undergone sepsis evaluations. In our study, 83% of the asymptomatic term neonates with EONS who did not meet criteria for sepsis evaluations at delivery developed symptoms after delivery within 24 hours. One report showed that 95% of term neonates with GBS EONS, despite their mothers receiving GBS prophylaxis, exhibited clinical signs of infection within 24 hours.[7] The consequences for the short delay in evaluation and treatment are not fully known.

A recent population-based study on all infants who were evaluated for sepsis found that about half was asymptomatic and underwent sepsis evaluations because of risk factors.[3] Among the asymptomatic infants who underwent sepsis evaluations, only 1% had likelihood of bacterial infection. This study also showed that elevated intrapartum temperature is a significant risk factor for bacterial infection in infants, especially those born to mothers who did not receive intrapartum antibiotics.

In the present time, dramatic decreases in incidence of GBS EONS have occurred because introduction of intrapartum antibiotic prophylaxis, especially after publication of guidelines that advocated either a screening-based or risk-based prevention strategy for early-onset GBS disease.[14–16] When the screening-based protocol was used, no cases of documented GBS EONS occurred in one study of over 3000 women screened.[17] As incidence of GBS EONS is decreasing, identification of term neonates with non-GBS EONS may become more important. In our study, term neonates with non-GBS EONS were more likely to be symptomatic at delivery than neonates with GBS EONS (64% vs 32%). More than half of the asymptomatic term neonates with non-GBS EONS were evaluated because of sepsis risk factors but only one (11%) of them was evaluated because of intrapartum fever, suggesting that fever may be less helpful in detecting term neonates with non-GBS EONS. As efforts to decrease GBS EONS continue, it may be useful to reevaluate the role of intrapartum fever in detection of EONS in asymptomatic term neonates.

Previously, the usual mortality rate of 25% was quoted for neonates (both preterm and term) with sepsis.[5] In our study, we found that the prognosis for term neonates with EONS seems much better with only one death in a neonate with congenital anomalies for a mortality rate of only 1%. In addition, we found a high discharge to home rate of over 80% in term neonates with EONS. The low mortality rate and high discharge to home rate may be the result of rigorous sepsis evaluations and early treatment.

We must stress certain limitations of our study. We have identified the population of term neonates with EONS but did not study controls (term neonates without EONS). As we did identify all cases of sepsis, we are able to calculate rates of EONS among term births. However, as we did not study term neonates without EONS, we cannot examine the frequency of maternal intrapartum fever in term neonates without EONS and cannot address the number of additional sepsis evaluations generated by using intrapartum fever as a criterion for sepsis evaluations. We showed that intrapartum fever increases sensitivity in identifying term neonates with EONS but we are unable to calculate specificity and positive and negative predictive values of intrapartum fever for EONS.

A majority of term neonates with EONS are asymptomatic at delivery and two-thirds of them was evaluated because of sepsis risk factors. Although intrapartum fever is associated with use of epidural analgesia in women with term deliveries and may be less specific as a risk factor, we found that if intrapartum fever were ignored, over a quarter of asymptomatic term neonates with EONS would not have been evaluated for sepsis immediately after delivery. Most of these neonates may have developed symptoms suggestive of infection sometime after delivery, but the consequences for the short delay in evaluation and treatment are not fully known. The discovery of a marker for chorioamnionitis, instead of relying on clinical symptoms such as fever, would be

invaluable and possibly lead to a decrease in sepsis evaluations and antibiotic treatment in neonates.

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