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Intrapartum Antibiotic Prophylaxis Increases the Incidence of Gram-Negative Neonatal Sepsis

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ABSTRACT

Objective: To investigate the influence of the increased use of intrapartum chemoprophylaxis on the incidence of vertically transmitted neonatal sepsis.

Methods: Multiple institutional databases were queried for the number of cases in which intrapartum antibiotics were used, the obstetric risk factors that were present, and the number of resultant cases of neonatal sepsis that occurred for deliveries from 1992 through 1997. Intrapartum antibiotic use was compared between the first and fourth quarter of 1997. Comparisons were made between the years 1992–1996 and 1997 for the incidence of the various pathogens causing neonatal sepsis; group B streptococcus (GBS), gram-negative sepsis, and others.

Results: We found a significant increase in intrapartum chemoprophylaxis between the first and fourth quarters of 1997 corresponding to the increased physician awareness of published guidelines. As expected, the incidence of neonatal GBS sepsis was drastically reduced (from 1.7/1000 live births to 0 in 3730 births, $P = 0.02$). Unfortunately, there was a concomitant increase in the incidence of gram-negative sepsis (0.29/1000 vs. 1.3/1000, $P = .02$). The overall incidence of neonatal sepsis remained unchanged (2.7/1000 vs. 2.1/1000, $P = .69$).

Conclusions: Published guidelines have encouraged physicians to increase the use of intrapartum chemoprophylaxis to reduce vertical transmission of GBS. This study confirms the efficacy of this approach. Unfortunately, this reduction comes at the cost of increasing the incidence of ampicillin-resistant gram-negative neonatal sepsis with a resultant increased mortality. These data provide compelling evidence that the policy of providing ampicillin chemoprophylaxis in selected patients needs to be reconsidered. Infect. Dis. Obstet. Gynecol. 7:210–213, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS

group B streptococcus, prophylaxis, neonatal sepsis, ampicillin, Enterobacteriaceae

While gram-negative neonatal sepsis (GNNS) has long been recognized as a clinical entity, it has been largely overshadowed in the last decade by discussions regarding group B streptococcal (GBS) neonatal sepsis. This is primarily a result of the historically higher incidence of GBS than GNNS. In July 1996, a communication was issued from the Centers for Disease Control and Prevention (CDC)[1] that recommended providing intrapartum chemoprophylaxis for the prevention of neonatal GBS. While there were other recommendations that preceded this, namely those of the American Academy of Pediatrics[2] and the American College of Obstetricians and Gynecologists,[3] the CDC's recommendation may have lessened some of the confusion in this area for some professionals.

In our center, clinical practice began to change following the CDC communication, with an increased use of intrapartum antibiotics. Two years

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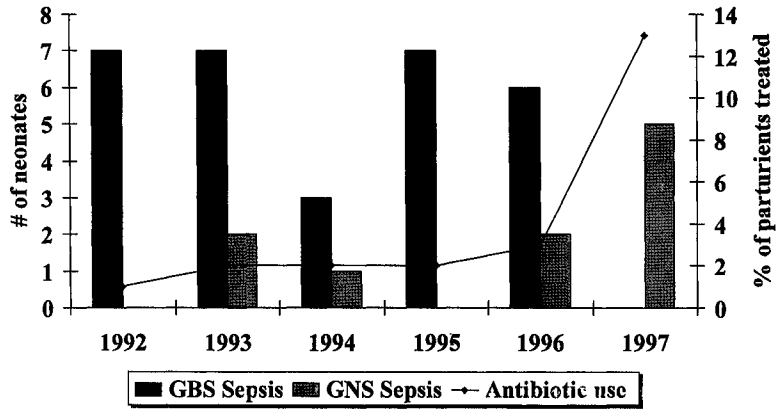

Fig. 1. Incidence of neonatal sepsis and intrapartum antibiotic use. GNS, gram-negative neonatal sepsis.

later we reviewed the impact of this change in clinical practice on the incidence of newborn GBS and GNNS by examining the perinatal statistics in our institution for the past 6 years. Specifically, we examined the prevalence of intrapartum antibiotic use and the incidence of GBS and GNNS prior to and subsequent to the CDC recommendation.

SUBJECTS AND METHODS

Early neonatal sepsis was defined as a positive blood and/or cerebrospinal fluid culture within the first 7 days of life. The Infection Control Surveillance database was queried for all such cases of neonatal sepsis with identification of the causative organism. Neonatal morbidity and mortality statistics and maternal data were obtained by querying our proprietary computerized perinatal database of 20,981 consecutive live births from January 1, 1992, through December 31, 1997.

The incidence of obstetric risk factors known to be associated with neonatal sepsis was also specifically reviewed for this time period. The risk factors that were recognized as relevant to this review included preterm delivery, prolonged rupture of membranes (>18 hr), prior urine culture positive for GBS, and intrapartum fever. Cases of chorioamnionitis were not excluded from the analysis.

Antibiotic usage was ascertained by querying the hospital's pharmacy information system for antibiotics administered in the labor and delivery suites. Individual chart reviews were performed for those cases with pharmacy ampicillin orders in which no risk factor was identified in the computer record to determine the actual risk factor(s) for these patients. The computer record was then appropriately updated as a result of the chart review. The remainder of the patients who received antibiotics in labor and delivery and who had risk factors prospectively identified were confirmed as having received intrapartum antibiotics.

A comparison was then made between the incidence of GBS and GNNS for the years 1992 through 1996 and that occurring in 1997, the first full year following the publication of the CDC guidelines. The relative use of intrapartum antibiotics during those two time periods, 1992–1996 and 1997, was compared as well.

Chi square analysis was used for comparisons of these discrete variables using the shareware computer program, Epistat.

RESULTS

The total number of deliveries, incidence of risk factors and neonatal sepsis, and percentage of patients receiving intrapartum antibiotics were reviewed for each quarter of 1997. The percentage of patients with one or more risk factors remained stable throughout 1997, with 27% in the 1st quarter and 27% in the 4th quarter. The percentage of patients who received antibiotics while in labor for their deliveries, however, increased significantly from the 1st quarter (3%), reflecting the level of use prior to 1997, to the 4th quarter (16%), $P = 0.00001$. This is depicted in Figure 1.

There were 21,569 deliveries from 1992 through 1997, yielding 17,251 live births for the years 1992 through 1996 and 3,730 live births during 1997. Data were divided into two groups: pre-1997 and 1997 deliveries. There were 30 cases of GBS during the pre-1997 period, for an incidence of 1.7/

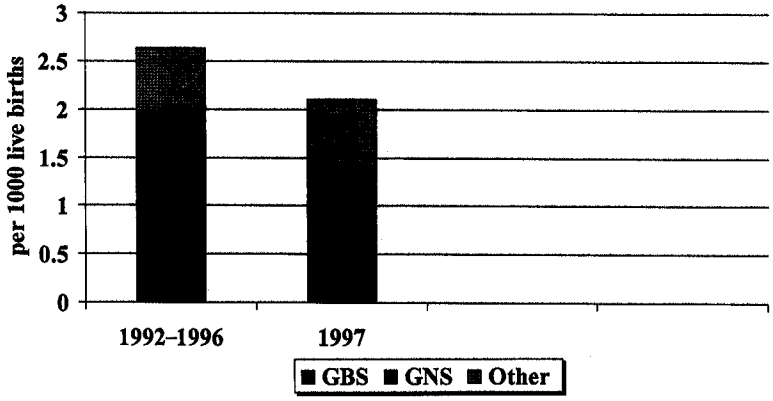

Fig. 2. Incidence of neonatal sepsis by pathogen. GNS, gram-negative neonatal sepsis.

TABLE 1. Cases of GNNS during 1997

ID	Delivery date	Gestational age	Risks	Prophylaxis given?	Organism	Outcome
1	1/11/97	27 wk	Yes	Yes	*Citrobacter* (ampicillin resistant)	Died
2	6/17/97	34 wk	Yes	No	*Klebsiella* (ampicillin resistant)	Died
3	8/5/97	24 wk	Yes	Yes	*Klebsiella* & *Enterobacter* (ampicillin resistant)	Discharged
4	9/20/97	28 wk	Yes	Yes	*E. coli* (ampicillin resistant)	Died
5	10/21/97	38 wk	No	No	*E. coli* (ampicillin resistant)	Discharged

1000 live births.[4] Five cases of GNNS occurred during that same period, for an incidence of 0.29/1000 live births. During 1997, coincident with the increased use of intrapartum antibiotics, there were no cases of GBS and five cases of GNNS (1.3/1000 live births). This represents a significant decrease of GBS rates (from 1.7 to 0/1000 live births, $P = 0.02$) with a concomitant 4.5-fold increase in GNNS cases (from 0.29 to 1.3/1000 live births, odds ratio = 4.63 with 95% confidence limits of 1.22 and 17.57, $P = 0.02$). The total number of cases of neonatal sepsis, including organisms other than GBS and GNNS (eg, enterococcus, staphylococcus), did not vary from pre-1997 to 1997 (2.7/1000 live births for 1992–1996, and 2.1/1000 live births in 1997, $P = 0.69$; see Fig. 2).

The individual cases of GNNS during 1997 are listed in Table 1. There were three deaths among the five cases of GNNS in 1997, for a mortality rate of 60%. Four of the five cases (80%) had risk factors for which three of the mothers received antibiotic prophylaxis with ampicillin. It could not be determined whether or not the other two mothers had received antibiotics antepartum. All pathogens recovered from the positive blood cultures in the neonates were resistant to ampicillin.

DISCUSSION

Intrapartum antibiotic use in our institution increased dramatically following the publication of the CDC guidelines. It is not clear why there was so little chemoprophylaxis provided prior to this, given the recommendations of other organizations preceding the CDC's recommendations. Our department provides care to both public and private patients, from both resident and private attending physicians, and there has been no consistently applied protocol for GBS prophylaxis applied to patients presenting to labor and delivery by the providers in our institution. Nonetheless, the vast majority of providers now give GBS chemoprophylaxis based on risk factors seen on presentation in labor. In addition, the antimicrobial choice has always been ampicillin, except for patients with intrapartum fever, in which case, cefoxitin is typically provided (despite the fact that the CDC[1] suggests that penicillin G is the preferred choice of a chemoprophylactic agent).

With the increased rate of intrapartum chemoprophylaxis in our institution, we observed a significant decrease in the incidence of GBS neonatal sepsis, as expected. Unfortunately, this was accom-

panied by a corresponding rise in the incidence of GNNS. It should also be noted that the overall incidence of neonatal sepsis remained unchanged following this increased intrapartum chemoprophylaxis.

In our institution, *Escherichia coli* isolates are resistant to the main beta-lactam antibiotic used, ampicillin, at least 50% of the time, with the other Enterobacteriaceae species often having an even greater resistance to ampicillin. One can then postulate that ampicillin may select for the growth of potentially pathogenic gram-negative bacilli, generally known to colonize the female lower genital tract and act as the reservoir for organisms that may subsequently cause the vertically transmitted neonatal sepsis. This may indicate a causal linkage between increased perinatal ampicillin use and increased incidence of GNNS. Our findings appear similar to those reported by McDuffie et al.[5] and further justify the recommendations offered by Amstey and Gibbs[6] that penicillin be used instead of ampicillin for GBS chemoprophylaxis. It should be emphasized that we found the mortality rate from GNNS (60%) to be 10-fold higher than that of GBS (6.7%), a circumstance not unlike that found elsewhere.[7,8]

In conclusion, the increased use of intrapartum ampicillin has, as predicted, decreased the rate of neonatal GBS sepsis in our institution. However, this has been accomplished at the cost of increasing GNNS, with attendant increased morbidity and mortality. This finding should cause concern for those health care providers responsible for preventing and treating infections of the perinate, and we believe these associations merit further investigation. If these findings are confirmed elsewhere, it may be time to reexamine our policies on intrapartum chemoprophylaxis, as they may be doing our neonates more harm than good.

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