abstract

The updated Guidelines on Prevention of Perinatal Group B Streptococcal Disease, issued by the Centers for Disease Control and Prevention, actually represent the mainstay in the prevention of neonatal early-onset group B streptococcal (GBS) sepsis. According to these guidelines, patients with possible preterm delivery are screened for GBS colonization and offered intrapartum prophylaxis only if they enter preterm labor or experience preterm premature rupture of the membranes. Nonetheless, the fulfillment of these recommendations seems to be suboptimal in clinical practice, as it is heavily influenced by the knowledge of the colonization status. We report here 2 cases of blood culture–proven, early-onset neonatal GBS sepsis involving preterm infants delivered by mothers who had midtrimester cervical insufficiency and bulging membranes. Midtrimester acute cervical insufficiency strongly predicts preterm delivery. These women are liable to miss intrapartum antibiotic prophylaxis because they typically have shorter labor, and the test results for GBS status are unlikely to be available before delivery. We believe that women with midtrimester cervical insufficiency and bulging membranes should be screened for GBS infection soon after hospital admittance if the gestational age is close to the threshold of fetal viability. A timely diagnosis of GBS colonization may not only increase the number of patients receiving targeted intrapartum antibiotic prophylaxis but would also allow consideration of the administration of antepartum antibiotic prophylaxis. Indeed, as further outlined in this report, GBS intraamniotic infection may dramatically occur before the onset of preterm labor or preterm premature rupture of the membranes.

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AUTHORS: Fabio Natale, MD, Roberto Brunelli, MD, Bianca Bizzarri, MD, Antonella Castronovo, MD, and Mario De Curtis, MD

a Dipartimento di Pediatria e Neuropsichiatria Infantile, and b Dipartimento di Scienze Ginecologico-Ostetriche e Scienze Urologiche, “Sapienza” University of Rome, Rome, Italy

KEY WORDS
cervical insufficiency, early-onset sepsis, group B streptococcus, preterm infant

ABBREVIATIONS
CI—cervical insufficiency
DOL—day of life
GBS—group B streptococcal
IAP—intrapartum antibiotic prophylaxis
PL—preterm labor
pPROM—preterm premature rupture of the membranes

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Address correspondence to Fabio Natale, MD, Neonatal ICU, Department of Pediatrics and Child Neuropsychiatry, “Sapienza” University of Rome, V.le Regina Elena 324-00161, Rome, Italy. E-mail: fab.natale@libero.it

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Over the past 4 years at our tertiary perinatal center, we have observed 3 cases of blood culture–proven, early-onset neonatal sepsis due to group B streptococcal (GBS) infection (incidence: 0.45/1000 live births per year). Two of the 3 cases involved preterm newborns delivered by women with midtrimester cervical insufficiency (CI).

CASE REPORT 1
A 30-year-old woman, gravida 2 para 1, was admitted to our center at 23 and 5/7 weeks with a diagnosis of CI; cervical dilation was 3 cm, and the membranes were bulging beyond the external uterine os. A decision was made by the senior obstetrician to insert a rescue cerclage. Recto-vaginal screening for GBS was not conducted. Perioperative intravenous antibiotic prophylaxis (ampicillin/sulbactam) was administered, but tocolysis was not performed. At 25 and 3/7 weeks, the patient underwent an emergency cesarean delivery due to the occurrence of a grade 2 placental abruption (fetal bradycardia).

A 932-g female infant was delivered; due to persistent bradycardia despite intubation, bag ventilation, and chest compressions, epinephrine was administered via an umbilical venous catheter with a persistent increase in heart rate. The Apgar score was 1 at 1 minute, 3 at 5 minutes, and 7 at 10 minutes. pH on arterial cord blood was 7.11 with a base excess of $-13.9 \text{ mmol/L}$. Hyaline membrane disease was treated by using assisted ventilation, supplemental oxygen, and natural porcine lung surfactant administration. A blood culture was obtained soon after birth; pending the results, empiric antibiotic therapy (ampicillin and gentamicin) was started. Results of laboratory tests performed on the first day of life (DOL) revealed high C-reactive protein levels ($3.5 \text{ mg/dL}$) and thrombocytopenia ($116 \times 10^3 / \text{L}$). On DOL 2, a head ultrasound documented a second-degree left intraventricular hemorrhage (according to Volpe’s classification) that was absent the previous day. On DOL 3, the blood culture grew ampicillin-sensitive Streptococcus agalactiae, while cerebral hemorrhage rapidly progressed to a third degree in the left ventricle and to a third degree plus intraparenchymal involvement in the right hemisphere. On DOL 4, the newborn’s clinical conditions rapidly deteriorated, and she died. The pathology report on the placenta was unremarkable, except for the presence of clusters of bacteria and inflammatory changes in the amniotic membranes.

CASE REPORT 2
A 34-year-old woman, gravida 3 para 2, was admitted at 27 and 0/7 weeks with a diagnosis of CI. Given the gestational age, advanced cervical dilation (5 cm), and presence of protruding membranes through the external uterine os, it was decided not to insert a rescue cerclage. Maternal screening for GBS was not obtained nor was tocolysis performed.

At 29 and 0/7 weeks of gestation, a 1520-g female infant was delivered by emergency cesarean delivery due to persistent (96-minute) severe fetal tachycardia (heart rate >180 beats per minute). The Apgar score was 3 at 1 minute, 5 at 5 minutes, and 7 at 10 minutes. pH on arterial cord blood was 7.05 with a base excess of $-12.7 \text{ mmol/L}$. Hyaline membrane disease was treated by using assisted ventilation, supplemental oxygen, and natural porcine lung surfactant administration. Soon after blood culture sampling, empiric antibiotic therapy was instituted (ampicillin/gentamicin). The newborn’s clinical course was complicated on DOL 1 by the onset of septic shock and acute renal failure; these were successfully treated by use of continuous intravenous infusion of dobutamine and furosemide, with progressive resolution in the following days. Altered prothrombin time (39.0 seconds) and the international normalized ratio (3.69) were normalized by using fresh frozen plasma infusion. C-reactive protein progressively decreased from 8.6 mg/dL on DOL 1 to normal values on DOL 6. Conversely, the infant’s white blood cell count was normal on DOL 1 ($16.6 \times 10^9 / \text{L}$) but progressively increased to its highest value on DOL 4 ($58.4 \times 10^9 / \text{L}$).

Acerebral intraventricular hemorrhage (second- and third-degree in the right and left ventricles, respectively) was first recorded on DOL 2. On DOL 3, the blood culture grew ampicillin-sensitive $S$ agalactiae, and a triventricular posthemorrhagic hypertensive hydrocephalus began to develop. On DOL 21, a ventriculoperitoneal shunt was placed, based on the evidence of a significant decrease in blood flow in the anterior and median cerebral arteries. On DOL 75, cerebral MRI documented the correct positioning of the shunt and a dilation of the entire supratentorial ventricular system (particularly relevant at the level of the occipital horns); in addition, the white matter appeared markedly hypotrophic. The patient is now 3 years old and suffers from spastic diplegia.

DISCUSSION
Because preterm infants are at high risk for GBS early-onset sepsis, and missed opportunities for prevention continue to be reported, these cases have prompted us to speculate about possible implementations of the current guidelines.

Preterm birth is a syndrome comprising preterm labor (PL), preterm premature rupture of the membranes (pPROM), and CI, (ie, a decrease in cervical structural competence occurring in the absence of uterine contractions). The true prevalence of CI, due to the multiple and
potentially overlapping causes of preterm delivery and to the lack of a widely agreed definition for diagnosis, is difficult to establish. Nonetheless, CI reportedly occurs in ~1% of the obstetric population and up to 8% of patients with recurrent midtrimester losses, and is considered responsible for ~5% of extremely preterm deliveries (<28 weeks).

A clear inverse relationship between a short cervix and preterm delivery has long been established. When midtrimester sonographic cervical length is 0 mm, one-third of patients deliver within 2 weeks, median diagnosis-to-delivery interval is 3 weeks, and only 25% of patients reach the 32 weeks of gestation. Patients with midtrimester CI/bulging membranes, due to the almost certain preterm delivery and the simultaneous presence of a variable time interval between admittance and delivery, represent an ideal subset of patients for targeted intrapartum antibiotic prophylaxis (IAP).

The recently updated Guidelines on Prevention of Perinatal Group B Streptococcal Disease, issued by the Centers for Disease Control and Prevention, state that GBS screening should be performed in all patients who have an established diagnosis of PL or pPROM, and that IAP should always be provided, pending culture results. Unfortunately, the implementation of these recommendations is suboptimal; in clinical practice, the administration of IAP is highly influenced by the awareness of the maternal colonization status, decreasing from 84.5% to 63.4% in patients with known or unknown colonization, respectively.

Patients with CI/bulging membranes, screened according to the present guidelines, are prone to fail to improve with IAP because they typically have shorter labor and the results of their screening are usually unavailable before delivery.

Therefore, we propose that patients with CI/bulging membranes be screened for GBS soon after hospital admittance if the gestational age is close to the threshold of fetal viability. This approach could increase the number of patients receiving targeted IAP through the timely detection of a possibly positive GBS colonization; of note, this screening could be done at no additional costs, involving a mere anticipation of the screening procedure already scheduled.

The adoption of an early screening policy could also allow the possibility of considering an antepartum prophylaxis (ie, antibiotic treatment before the onset of PL or the occurrence of pPROM).

Sound evidence that antibiotic treatment of women who have CI and intact membranes could alter the outcome of pregnancy and of the newborn infant is currently unavailable: to our knowledge, only 1 study has suggested that parenteral antibiotic treatment may sometimes reduce the intensity of the intraamniotic inflammatory response, prolonging the time interval to delivery and improving neonatal outcome. Nonetheless, we believe that antepartum GBS antibiotic prophylaxis may reasonably be useful in the subset of patients with CI/bulging membranes on the basis of the following evidence:

1. Women with CI and bulging membranes have a very high rate (81%) of intraamniotic inflammation (a risk factor for adverse neonatal outcome) and up to 50% of them present with microbial invasion of the amniotic cavity.

2. Amnion cells constitute a relatively competent barrier to microbial penetration, but many microorganisms, including GBS, can pass through intact membranes, inducing an inflammation-dependent disruption of amnion integrity.

3. Transit through amnion cells may be particularly expedited across the protruding membranes due to the absence of the antibacterial properties of the cervical mucus plug.

4. Although the association between antepartum GBS colonization and preterm delivery does not seem significant, recent evidence in primates suggests that CI might represent a marker of GBS-dependent chorioamnionitis.

5. Some intravenous antibiotics (penicillin and ampicillin) are highly effective in preventing vertical transmission of GBS (through vaginal decolonization), as measured by infant colonization or by protection against neonatal early-onset disease.

CONCLUSIONS

Patients with midtrimester CI/bulging membranes, due to the strong likelihood of preterm delivery and the simultaneous presence of a variable time interval between admittance and delivery, represent an ideal subset of patients in whom to increase targeted IAP.

We propose the following approaches. A recto-vaginal swab for GBS should be promptly performed at admittance in patients with advanced midtrimester CI if the gestational age is close to the threshold of fetal viability, with the aim to increase GBS detection and targeted IAP. Also, if the results of the GBS culture are positive, antepartum antibiotic prophylaxis could be considered. Due to the dramatic burden related to a possibly intercurrent GBS intraamniotic infection, we believe that GBS vaginal decontamination could be attempted well before the onset of PL or pPROM.

Randomized controlled trials evaluating the efficacy of antepartum antibiotic prophylaxis must be performed before recommending such treatment.
REFERENCES


Cervical Insufficiency: A New Issue for Guidelines on Prevention of Perinatal Group B Streptococcal Disease?
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