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Group B Streptococcal Disease in a Newborn Infant After Negative Screen in a Pregnant Female Patient Taking Oral Antibiotics

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ABSTRACT

BACKGROUND: Group B streptococcus (GBS) is a leading cause of serious neonatal infection. Neonatal morbidity and mortality can be reduced by appropriate prenatal screening and intrapartum chemoprophylaxis.
CASE: A 26-year-old-primigravida at 37 weeks of gestation was admitted for induction of labor for mild preeclampsia at term with a favorable cervix. She was treated with oral antibiotics at 35 weeks for a recurrent urinary tract infection. Her GBS screen following the antibiotic treatment showed a negative culture. The patient, therefore, did not receive intravenous antibiotics during her induction of labor. The infant suffered from severe placental insufficiency and early onset neonatal GBS pneumonia and sepsis.
CONCLUSION: Oral antibiotics can cause a temporary negative culture in a GBS-colonized patient. Relying on a negative culture for management may not be appropriate in a patient treated with oral antibiotics.

INTRODUCTION

Between the late 1960s and the 1970s, group B streptococcus overtook Escherichia coli as the most important causal agent of meningitis and septicemia in newborns.[1] Although group B streptococcal syndrome has been studied extensively, the connection between colonization in the mother and infection in the infant is poorly understood; Isolation rates from mothers have been reported in the range of 15 to 40 percent.[2-4] Colonization of the vagina and rectum in the mother is more common than colonization of the cervix and the urinary tract.[1,5] Vaginal cultures taken serially during pregnancy may be intermittently positive.[3,6,7] The gastrointestinal tract may serve as a reservoir for chronic carriage of group B streptococcus.

Thirty to 70 percent of infants born to mothers with group B streptococcus colonization also become colonized at rectal, umbilical or oral sites. However, only 1 to 2 percent of infants born to colonized mothers become clinically infected. The reason for the low ratio of infected infants to colonized infants is still under investigation. A positive correlation has been found between the level of maternal colonization and the subsequent fate of the infant.[8]
Premature infants have a 10 to 15 times greater risk of acquiring group B streptococcal infection than full-term infants.[9] The greatly increased infection rate in premature infants may reflect their relatively immature defense systems.

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Because of the lowered activation of the classic complement pathway by bacteria in general, and by encapsulated bacteria in particular, the role of specific antibodies in defense against this infection is of great importance. It has been shown that 60 percent of transplacental IgG transfer takes place during the last quarter of pregnancy, so premature infants may not receive the full amount of Igg.[10] Although low infant antibody concentration has been correlated with disease, this cannot be the only factor involved, because most infants born to colonized women with low IgG levels remain well.[11]
In spite of the low infection rates, group B streptococcal disease is responsible for 2,000 neonatal deaths in the United States each year. Of every 1,000 newborns, two to three develop the early-onset sepsis/pneumonia syndrome or the late-onset meningitis syndrome of group B streptococcus infection. These syndromes carry 15 to 50 percent mortality rates and, of the meningitis survivors, nearly 50 percent have some permanent neurologic residual deficit.[12,13]

In recent studies,[14] mortality rates have been lower than previously reported. The decline in mortality is probably caused by a combination of factors, including intrapartum antibiotic treatment, earlier recognition of group B streptococcal sepsis and improved neonatal care.

The attack rate may rise to 10 in 1,000 in infants born to mothers with vaginal colonization at birth. Rates as high as 40 in 1,000 have been associated with prematurity, prolonged rupture of the membranes, maternal fever or frank chorioamnionitis during labor, maternal history of a previous infected child, or multiple gestation.[2,8,15]
Maternal infection is also a substantial problem, giving rise to chorioamnionitis, puerperal endomyometritis (especially after cesarean section) and urinary tract infection.[16]

The diagnosis and treatment of perinatal group B streptococcal infection continue to be major problems for physicians who care for mothers and infants. Newer tests for early detection of infection may improve the neonatal prognosis, which is dismal once infection is established. Still remaining is much research into the virulence factors that allow some organisms to be highly invasive, while others produce only asymptomatic colonization.

Fetal growth is dependent on genetic, placental and maternal factors. The fetus is thought to have an inherent growth potential that, under normal circumstances, yields a healthy newborn of appropriate size. The maternal-placental-fetal units act in harmony to provide the needs of the fetus while supporting the physiologic changes of the mother. Limitation of growth potential in the fetus is analogous to failure to thrive in the infant. The causes of both can be intrinsic or environmental. The placenta can undergo structural and functional adaptations in response to an unfavorable maternal milieu. Such changes have been noted in both pathological and experimental scenarios of maternal anemia, undernutrition, and hypoxia. In human placentas that develop under conditions of hypobaric hypoxia, significant changes in fetal capillary volume (increased vessel diameter and length) and villus membrane thickness have been reported. These adaptations function to facilitate increased gaseous exchange between the maternal and fetal circulation. Hypoxia is probably a consequence of reduced trophoblast invasion of the decidua. Preeclampsia is an important clinical condition of altered placental growth and intrauterine growth restriction. Although the pathophysiology of this condition has not been fully elucidated, it has been established that the primary defect is one of shallow trophoblast invasion. Histochemical analysis of the placenta in preeclamptic pregnancies has shown increased proliferation of anchoring (noninvasive) trophoblasts and a decreased fraction of extravillus (invasive) trophoblasts.

CASE REPORT

A 26-year-old primigravida at 37 weeks of gestation was admitted for induction of labor for mild preeclampsia at term with a favorable cervix. The patient had mildly elevated blood pressures in the third trimester and 340 mg of proteinuria in a 24-hour specimen. The patient's only other pregnancy complication was a recurrent urinary tract infection. After a negative first-trimester screen for asymptomatic bacteriuria, the patient complained of urinary frequency and discomfort at 22 weeks of gestation. The urinalysis revealed moderate leukocyte esterase and 2+ bacteria. She was treated with a 7-day course of nitrofurantoin with full resolution of symptoms. Urine culture on the clean catch specimen showed mixed organisms. At 35 weeks of gestation, the patient had a recurrent urinary tract infection with similar symptoms and urinalysis findings. She was treated with a course of azithromycin to cover for concurrent respiratory symptoms. The patient received an initial dose of 500 mg, followed by 4 additional doses of 250 mg per day. The urine culture gathered before antibiotic therapy again failed to isolate a causative organism. Group B streptococcus was not identified in either urine culture. At 36 weeks, 4 days after the completion of her antibiotic treatment, the patient had a negative GBS culture. The culture was collected per the Center for Disease Control and Prevention (CDC) recommendations to include the

vaginal introitus, perineum, and rectum. The swabs were inoculated into a selective broth medium, and GBS was not identified after both 24 and 48 hours of incubation.

After admission, oxytocin was initiated for labor induction and magnesium sulfate for seizure prophylaxis. The patient progressed to 5 cm dilatation, but did not progress further, even with adequate contraction for 4 hours. Artificial rupture of the membranes produced turbid but non-foul-smelling amniotic fluid.

A fetal scalp electrode recorded a baseline fetal heart rate of 190 beats per minute, with decreased long- and short-term variability. Deep, variable decelerations occurred with regularity. Fetal scalp venous pH was 710.
While preparations were being made for an immediate cesarean section, the patient rapidly delivered a male infant weighing 2,183 g (4 lb, 13 oz). The infant's appearance was consistent with 37 weeks' gestation. Apgar scores were 1 at one minute, 5 at five minutes and 5 at 10 minutes. Umbilical artery pH was 708.

The infant was pale and floppy, and grunting, flaring and retractions were noted immediately in the delivery room. His vital signs were as follows: respirations, 72 per minute; heart rate, 170 beats per minute; blood pressure, 50 flush, and temperature, 37.4 C . The infant was placed in an oxygen hood. Measurements on arterial blood drawn from an umbilical artery line revealed the following values: pH 707; partial pressure of carbon dioxide 48 mm Hg; partial pressure of oxygen 44 mm Hg; bicarbonate 2.5 mmol per L.

The infant was intubated. Chest films revealed a pattern of bilateral interstitial and alveolar infiltrates with air bronchograms. Cultures were drawn, and the infant was immediately given ampicillin and gentamicin.

Despite adjustments in the ventilator settings, oxygenation of the infant could not be satisfactorily maintained. Severe acidosis, oliguria and a clinical picture of disseminated intravascular coagulation supervened. Pressors were required to maintain the infant's blood pressure. Cardiac arrest occurred at 15 hours of life, and resuscitation was unsuccessful. At autopsy the lungs were found to have a "liver-like" appearance, and there were bilateral bloody pleural effusions and diffuse petechial hemorrhages of the surfaces of other internal organs. Cultures of the cut surfaces of the lung, as well as blood from the infant's heart, grew group B hemolytic streptococcus (Streptococcus agalactiae). Vaginal and rectal cultures obtained from the mother during labor also showed a heavy growth of group B streptococcus.

DISCUSSION

Neonatal group B streptococcal disease is manifested in two forms. The most common form, and the one with the most serious prognosis, is early-onset disease (symptoms appearing within seven days of birth). Although seven days is an arbitrary limit for early-onset disease, most cases are detected within 24 hours of birth. It has been shown that approximately two-thirds of cases of group B streptococcal infection are early onset. Early-onset disease is found with equal distribution in both male and female infants.[17]

As can be demonstrated by serotyping colonized mothers and infants, all transmission of early-onset disease is vertical. Evidence suggests that there are two models of transmission of the disease from mother to infant. In one model, infants are born with low Apgar scores and pulmonary infiltrates, while in the second model, infants are born healthy but develop symptoms gradually several days after birth.[18] This difference indicates that infection can occur either by the intra-amniotic route or directly, during passage through the birth canal. Of infants in one study,[19] 56 percent were symptomatic at birth or within six hours, suggesting that infection in utero may be responsible for a high percentage of early-onset group B streptococcal infections.

Symptoms developing after seven days and up to three months of age are considered the sign of late-onset disease. Some infants clearly acquire the infection from nonmaternal sources. In one study,[20] only 7 of 21 cases of late-onset infection occurred in infants whose mothers had measurable colonization at the time of delivery. Evidence of transmission after birth is conflicting, however, because only 4.3 percent of neonates who had negative cultures at birth had positive cultures of the mucous membranes after two months.[21]

The disparity between these and other studies may derive from a difference in nursery populations. In situations in which infants whose mothers had heavy colonization were placed in crowded nurseries in close proximity to noncolonized infants, the rate of infant-to-infant spread was high. The major determining factor in horizontal transmission was shown to be a high nursery population density, combined with relatively few nursing personnel.[22]

Culture is the usual method of diagnosing group B streptococcal infection and is greatly enhanced by the use of selective broth media (i.e., Todd-Hewitt broth with gentamycin and nalidixic acid), which inhibit

concomitant growth of gram-negative flora. Simply plating specimens onto blood agar plates results in failure to detect the organism in more than 50 percent of cultures.

The Centers for Disease Control and Prevention (CDC) [23], the American Academy of Pediatrics (AAP), and the American College of Obstetricians and Gynecologists (ACOG) recommend that all pregnant women — with two exceptions — be screened for GBS at 35 to 37 weeks.

However, women who've had a child with a GBS infection in the past do not need to be screened because they're already known to be at high risk and will automatically be treated during labor. The same goes for women who are found to have GBS in their urine during their pregnancy. If this happens, the pregnant woman will be treated with oral antibiotics right away. And she'll automatically get intravenous antibiotics during labor because having GBS in her urine is a sign that she has a lot of GBS in her genital tract. Although oral antibiotics will take care of the bacteria in the urinary tract, some bacteria may remain in the genital tract or return there later. The only case in which she would not need the antibiotics is when she has planned a cesarean section that happens before she goes into labor. Oral antibiotics can cause a temporary negative culture in a GBS-colonized patient. Relying on a negative culture for management may not be appropriate in a patient treated with oral antibiotics. Additional studies are necessary to elucidate the effects of oral antibiotics on GBS.

Preeclampsia causes placental damage that results in uteroplacental insufficiency. The pathogenic mechanism is thought to be a failure of trophoblastic invasion by maternal spiral arterioles by 20 to 22 weeks of gestation.This failure causes luminal narrowing and medial degeneration, leading to diminished blood flow to the developing infant. Consequently, these infants fail to grow normally.

The 'Fetal origins hypothesis' states that individuals born small because of malnutrition are predisposed to adult diseases. Fetal malnutrition has two main causes, poor maternal nutrition and placental insufficiency. A distinction between these causes is important because it is likely that maternal nutrition has been sufficient in the majority of populations in which the fetal origins hypothesis has been tested. Thus, placental insufficiency is a more reasonable cause of reduced fetal growth in adequately nourished populations. Placental insufficiency is mainly due to inadequate vascular adaptation at the uteroplacental interface ('poor placentation'). Among women with placental insufficiency syndromes such as pre-eclampsia and 'idiopathic' intrauterine growth retardation, there is an increased prevalence of risk factors for cardiovascular diseases. Maternal cardiovascular risk factors may therefore increase the risk of adult diseases in the offspring both through direct inheritance and by interfering with uteroplacental vascular adaptation. The latter may result in placental insufficiency and fetal growth retardation that by itself could cause adult disease (as the Fetal origins hypothesis states). Alternatively, the association between low birth weight for gestational and adult disease could be an epiphenomenon, leaving inheritance as the main explanation for the fetal origins hypothesis, in adequately nourished populations [24].

Since its emergence 25 years ago, group B streptococcus has become recognized as a cause of serious illness in newborns, pregnant women, and adults with chronic medical conditions. Heavy colonization of the genital tract with group B streptococcus also increases the risk that a woman will deliver a preterm low-birthweight infant. Early-onset infections (occurring at <7 days of age) are associated with much lower fatality than when they were first described, and their incidence is finally decreasing as the use of preventive antibiotics during childbirth increases among women at risk. New serotypes of group B streptococcus have emerged as important pathogens in adults and newborns. Clinical and laboratory practicesin obstetrics, pediatrics, and clinical microbiologyhave an impact on disease and/or its prevention, and protocols established at the institutional level appear to be critical tools for the reduction of perinatal disease due to group B streptococcus. Since intrapartum antibiotics will prevent at best only a portion of the full burden of group B streptococcal disease, critical developments in vaccine evaluation, including study of polysaccharide-protein conjugate vaccines, offer the potential for enhanced prevention in the relatively near future [25].

Infection of the fetus and newborn infant poses unique challenges in both diagnosis and management. Transplacental infections can result in fetal loss/abnormalities and intrauterine growth restriction. Such infections usually persist and may be evident or asymptomatic at birth. Some of the latter cases may develop late symptoms such as Toxoplasma choroidoretinitis. Diagnosis remains difficult because clinical features lack specificity and because the immaturity of the neonatal immunity and the existence of maternal antibodies make serology hard to interpret. However, increasing use of polymerase chain reaction analysis and related techniques has resulted in increasingly accurate diagnosis. Interventions to reduce the burden of infection include maternal

avoidance of high-risk foods, mass immunization (rubella), antenatal and post-natal treatment (HIV, Toxoplasma), neonatal immunization (hepatitis B) and avoidance of breast-feeding (HIV). The occurrence of early onset streptococcal infection cannot be fully suppressed with the use of screening policies.Early-onset neonatal sepsis (EONS) is almost exclusively caused by organisms acquired from the maternal genital tract and carries high mortality and morbidity. Vaginal antiseptic treatments have proved disappointing in preventing infection. After pre-term rupture of membranes, prophylactic antibiotic administration to the mother reduces the incidence of EONS. In any woman known to carry group B Streptococcus, intrapartum antibiotics can greatly reduce the incidence of EONS caused by this organism. Late-onset neonatal sepsis and acquired neonatal viral infections are usually acquired horizontally from the environment. The range of organisms is wide. Attention to infection control procedures in the nursery and judicious use of antibiotics to reduce the risk of emergence of antibiotic resistant bacterial or fungal infections are important [26,27].

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