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OBSTETRICAL CARE IN FUTURE PREGNANCIES AFTER FETAL LOSS IN GROUP B STREPTOCOCCAL SEPTICEMIA. A PREVENTION PROGRAM BASED ON BACTERIOLOGICAL AND IMMUNOLOGICAL FOLLOW-UP

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Among 22 mothers of infants infected with group B streptococci (GBS), 19 showed markedly low levels of antibodies against the infecting type. Three of the patients with low antibody levels went through a new pregnancy within 1 yr after they had lost an infant (2 patients) or experienced fetal death due to GBS (1 patient). They were still urogenital carriers of the type of GBS causing the previous infection, and their serum levels of type-specific antibodies remained low. All three went through a successful pregnancy following a prevention program comprising antibiotic treatment from the 28th wk of pregnancy.

fetal death; urogenital carriers of GBS; penicillin

INTRODUCTION

Early onset neonatal infection with group B streptococci (GBS) is one of the most serious and most frequently occurring infections in newborns (Eickhoff et al., 1964; Franciosi et al., 1973; Baker, 1977). The mortality rate is high, 50—75% (Eickhoff et al., 1964; Franciosi et al., 1973; Baker, 1977). The disease can affect infants of any gestational age, from the most immature to apparently healthy infants born at term. This is in contrast to other neonatal diseases with high mortality rates, e.g., idiopathic respiratory distress syndrome, or intracerebral hemorrhage, which occur almost exclu-

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sively among prematures. Furthermore, GBS can lead to intrauterine fetal death (Bergqvist et al., 1978) and may give rise to fetal distress during labor (Christensen et al., 1980b).

The early onset form of GBS infection may develop precipitately, and antibiotic therapy is often begun too late. Therefore, prophylactic administration of antibiotics to pregnant carriers of GBS or their infants has been tried (Siegel et al., 1980). Routine administration of parenteral penicillin at birth reduces the frequency of neonatal GBS infection, whereas diseases caused by other pathogens increase in frequency (Siegel et al., 1980). These findings do not speak in favor of generalized prophylactic measures in GBS carriers.

It has been shown that mothers of GBS-infected infants lack type-specific serum antibodies against the type of GBS infecting their infants (Baker and Kasper, 1976; Hemming et al., 1976; Christensen et al., 1980a; Vogel et al., 1980). However, not all infants of GBS carriers who lack type-specific antibodies become infected (Baker and Kasper, 1976; Hemming et al., 1976; Christensen et al., 1980a; Vogel et al., 1980), indicating that other factors may predispose to the disease. Despite our deficient knowledge about these factors it is possible to distinguish a group of women at high risk among the GBS carriers with low-type-specific antibody levels. This group consists of pregnant women who (1) have previously given birth to a baby with serious GBS infection or experienced intrauterine fetal death due to GBS; (2) are still carriers of the type of GBS causing the previous infection; and (3) have unaltered low levels of antibody against this type of GBS.

The present paper describes the successful obstetrical care of 3 women belonging to the risk group. Briefly, these patients were given antibiotics from the 28th wk of pregnancy and the treatment was continued in the baby after birth.

MATERIALS AND METHODS

Patients giving birth to infants with serious GBS infections

Specimens from 22 infants with serious infections and from their respective mothers were obtained from various parts of Sweden during the period of January, 1978 to December, 1980. Twenty of the infants fell ill within 48 h after birth, with GBS septicemia and/or meningitis (early onset type) while 2 fetuses were infected in utero, leading to stillbirth in pregnancy during weeks 23 and 35, respectively. Six (30%) of the 20 infants with early onset disease died from the infection.

GBS strains were isolated from blood and/or cerebrospinal fluid specimens in the 20 infants who contracted early onset GBS neonatal infection. The GBS strains from the fetuses which died in utero were isolated as the sole microorganism from all inner organs during sterile autopsy, performed as described by Christensen et al. (Unpubl. obs.). None of these fetuses showed malformations. GBS strains were also isolated from the urethra and/or cervix of each mother, and a serum specimen was obtained for quantitation of GBS antibodies.

Prospective study of pregnancy and delivery in 3 mothers who had previously given birth to infants with serious GBS infections or experienced intrauterine fetal death due to GBS

Obstetrical and neonatal care. The antenatal care of the 3 mothers comprised clinical examinations, blood pressure measurements, laboratory tests (hemoglobin, Wasserman, rubella-antibody titer and tests for albuminuria and glycosuria) including bacterial culture of the urine, fetal heart rate (FHR) and fundal height measurements. Ultrasound scanning was performed at least three times during the pregnancy, in weeks 8, 18 and 32. FHR recordings were obtained weekly from the 28th wk. During the first trimester, urethral and cervical specimens for culture of GBS using a selective broth (Baker et al., 1973) and serum specimens for antibody quantitation against GBS were obtained on one occasion. The GBS cultures were repeated from the 28th wk of pregnancy. Specimens were also taken weekly (using sterile cotton swabs) from the urethra and the cervix for culture of other potentially pathogenic bacteria (β-streptococci of other groups, *S. aureus*, *Enterobacteriaceae*, *Pseudomonas*, *Listeria monocytogenes*, *H. influenza*, etc.).

Treatment with V-penicillin (0.8 g twice daily) was started in the 28th wk and continued until delivery. If spontaneous labor did not occur at term, delivery was induced by amniotomy and oxytocin stimulation. During labor ampicillin was given intravenously (2 g every 6 h). The fetus and mother were supervised with electronic fetal monitoring.

Immediately after birth the infant was examined by a neonatologist, and specimens for bacteriological examinations were taken from the external ear, the throat and the umbilicus. The infant was transferred to the neonatal intensive care unit for observation during the first days of life. Treatment with cefalexin was started and continued for 4 wk, after which the infant was examined again.

Four weeks after birth, specimens for cultivation of GBS were again taken from the mother's urethra and cervix.

Microbiological examinations

The cultures and identification tests for potentially pathogenic bacteria were performed as described by Christensen et al. (Unpubl. obs.). Identification, grouping and typing of GBS were performed as described elsewhere (Christensen et al., 1980a). Antibodies to GBS types Ia, Ib, II and III were measured with radiolabelled protein A (Christensen et al., 1980a). In brief, the serum to be tested was absorbed with type II GBS before determination of antibodies against types Ia, Ib and III, and with type III GBS, when antibodies to type II were being measured. The absorbed serum was mixed with a standard suspension of the type of GBS to which antibodies were to be measured. The quantity of antibodies bound to the surface of the bacteria after washings was determined with protein A which reacts with the Fc part of human IgG subclasses 1, 2 and 4 (Kronvall and Williams, 1969). The antibody level was expressed as the radioactive protein A in counts per minute (cpm) bound to the bacteria after coating with serum.

The antibody levels measured were compared with those in sera from mothers found to be harboring types Ia, Ib, II and III in the urogenital tract and who gave birth to infants without signs of infection. The antibody levels among the controls were as follows. Against type Ia: 8100—17 000 cpm (mean 11 100 cpm); against type Ib: 17 000—28 000 cpm (mean 20 760 cpm); against type II: 12 500—23 000 cpm (mean 18 750 cpm); and against type III: 9000—31 000 cpm (mean 17 300 cpm). These results were based on tests of sera from 10 individuals for each type of GBS.

RESULTS

Serum levels of antibodies in 22 mothers giving birth to infants with early onset GBS diseases, or who had fetuses who died in utero due to GBS infection

GBS type Ia was isolated from 4 of the 20 infants with early onset septicemia and/or meningitis, type Ib from 4, type II from 2 and type III from 10 infants. Types II and III were isolated from each of the intrauterine-death fetuses.

All mothers harbored the same type of GBS in the urogenital tract as iso-

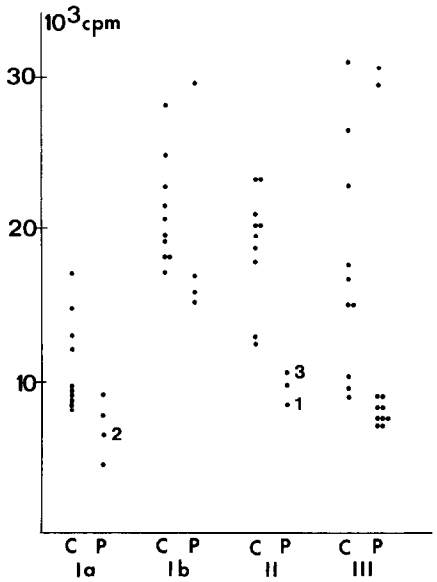

Fig. 1. Test of sera from mothers of infants with GBS sepsis and/or meningitis (P) and sera from mothers of infants who were healthy in the neonatal period (C). Each maternal serum was tested against the type of GBS infecting the corresponding infant, or that found in the urogenital tract of each mother giving birth to a noninfected infant. Ordinate: uptake of radiolabelled protein A on the bacteria after addition of serum. Ia, Ib, II and III indicate the bacteria against which antibodies were measured. 1, 2 and 3 indicate the serum levels of antibody in patients no. 1, 2 and 3, respectively.

lated from their respective infant or fetus; one mother carried an additional type.

The serum levels of antibodies against the type of GBS isolated from each individual patient are given in Fig. 1. All mothers of infants (or fetuses) infected with type Ia or type II had very low levels of type-specific antibodies against the respective type, when compared with the controls. Four of the 5 mothers of Ib-infected infants had low levels of type-specific antibodies against this type. The mother with a high level of antibodies to type Ib suffered from juvenile diabetes. Nine of 11 mothers of infants acquiring type III infections had low levels of antibodies against type III, while 2 mothers had relatively high levels. However, both infants had umbilical catheters inserted immediately after birth; of these, one infant was born in week 29 and the mother of the other infant was heavily ABO-immunized resulting in hemolytic disease in the infant.

Outcome of pregnancies following fetal wastage in GBS infection

Three of the patients listed above went through a new pregnancy after loss of an infant (2 patients) or a fetus (1 patient) due to GBS infection, and were checked and treated according to the prevention program.

CASE REPORTS

Case no. 1

This patient was a 28-yr-old gravida 4. She had experienced one spontaneous abortion in week 9 of pregnancy and gave birth to a healthy infant 3 years ago. One year before the present pregnancy she gave birth to an infant who died after 36 h of a type II GBS infection. Her serum antibody level against type II was very low immediately after the delivery (8100 cpm).

During the present pregnancy she was still a carrier of GBS type II in the urogenital tract and her antibody level was unchanged. Specimens taken from the urogenital tract during penicillin treatment showed a growth of GBS type II on one occasion after 3 wk of treatment; no other potentially pathogenic bacteria were isolated. Labor was induced in the 38th wk, and she gave birth to a boy of 2800 g, who was healthy and developed normally. Upon examination 4 wk after the delivery, GBS type II was again found in the urethral and cervical specimens.

Case no. 2

This patient was a 29-yr-old gravida 2. After normal development of the first pregnancy, she delivered a baby who died after 6 h of a type Ia GBS sepsis. GBS type Ia was also isolated from the urogenital tract of the mother, and she had low levels of antibodies against type Ia (6300 cpm) which remained low during the following pregnancy. During this pregnancy GBS type Ia could be isolated from the urogenital tract before treatment with penicillin was started, whereas the specimens obtained during the treatment were all negative. In the 39th week of pregnancy the patient gave birth to a

girl of 4200 g. The baby remained healthy throughout the neonatal period. Four weeks after the delivery GBS type Ia was again found in the urogenital tract of the mother.

Case no. 3

This patient was a 37-yr-old gravida 3 (one healthy infant). One year before the present pregnancy, she had experienced a late spontaneous abortion (week 23). Specimens from all inner organs of the fetus obtained at sterile autopsy revealed growth of GBS type II. No other microorganisms were isolated (including search for viruses, chlamydia and mycoplasmas). Her antibody level against type II GBS was low (1200 cpm) and remained so during the following pregnancy. GBS type II was also isolated from the patient's urogenital tract. Early in the present pregnancy she still carried GBS type II. GBS type II was isolated once during treatment and again after delivery. In the 34th wk, *E. coli* could be isolated from the cervical specimen, but apart from that, all specimens were negative.

DISCUSSION

In this investigation, a risk group of pregnant GBS-carriers was defined, and a program for prevention of serious fetal and neonatal GBS infection was instituted. The risk group was characterized by the following conditions. (1) The patient had previously given birth to an infant who had contracted GBS sepsis and/or meningitis, or she had experienced intrauterine fetal death due to GBS; (2) she was still a urogenital carrier of the type of GBS causing the previous infection; and (3) her serum antibody level against this type remained low. It follows that correct diagnosis of neonatal or fetal death is mandatory in order to detect members of this group, and that typing of isolated GBS is needed to monitor colonization and development of antibodies during future pregnancies.

In order to determine risk levels of GBS antibodies, we tested the sera from 22 mothers who had given birth to an infant with early onset GBS infection or who had experienced intrauterine fetal death due to GBS. The mortality rate in early onset disease among the infants was 30% (6 out of 20). In addition, 2 patients had a miscarriage due to antenatal infection. Nineteen of the 22 patients had low levels of antibodies against the infecting type of GBS, when compared with urogenital carriers of GBS having given birth to noninfected infants (Fig. 1). This observation, confirming our previous findings in 7 patients (Christensen et al., 1980a), is in agreement with several other investigations, in which a variety of antibody-quantitation techniques were used (Baker and Kasper, 1976; Hemming et al., 1976; Vogel et al., 1980). The 3 patients with high GBS antibody levels (Fig. 1) illustrate that other obstetrical and neonatal complications may overcome the immunity barrier.

Three of 8 patients who had lost their infant or fetus, were pregnant again within 1 yr. It was found that all 3 were still carriers of the type of GBS

causing the fatal infection. Furthermore, their serum levels of type-specific antibodies remained low. Thus all 3 fell within the risk group definition. Considering the unanimous reports on the importance of type-specific antibodies, we found it ethically impossible to design any form of placebo-controlled study on this patient category.

The purpose of the prevention program was to suppress GBS in the maternal urogenital tract and thereby minimize the risk of contamination of the newborn. Furthermore, we wanted to achieve a sufficiently high concentration of antibiotic in the fetus, in order to inhibit infection in utero; also, antenatal FHR recordings were taken weekly to discover intrauterine distress. One well-known risk of protracted administration of antibiotics is the possibility of selecting resistant strains. Penicillin was chosen for administration during pregnancy because of its low toxicity and the scant likelihood of selecting resistant strains, such as *Klebsiella* or *Pseudomonas*. Urethral and cervical specimens were taken weekly during pregnancy to ensure that no super-infection developed. With the exception of GBS, *E. coli* was the only potentially pathogenic bacterium isolated during treatment (found on one occasion in week 34 from the cervix of patient no. 3). Our observations demonstrate that it is not possible to eradicate GBS from the urogenital tract by administering penicillin. GBS was isolated on one occasion from each 2 patients during treatment. Furthermore, 4 wk after delivery, all 3 patients were carriers of the type of GBS isolated at the beginning of the pregnancy, although they denied that sexual intercourse had occurred since the delivery.

Ampicillin was given intravenously during the delivery in order to achieve a high concentration of antibiotic in the fetus (penicillin given intravenously would probably be equally protective). The administration of antibiotic to the newborn was continued, using cefalexin, which was chosen because of occasional outbreaks of *Klebsiella* on the neonatal ward. The infants were all culture-negative at birth and at 4 wk of age. No side-effects of the treatment of the mothers or infants were noted. Thus, the prevention program seemed to have been a success in the 3 patients.

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