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Maternal Group B Streptococcus Infection, Neonatal Outcome and the Role of Preventive Strategies

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A B S T R A C T

To determine the newborn infection rate with group B streptococcus infection (GBS) before and after American Academy of Pediatrics Protocol (AAP) implementation in Croatia, antenatal risk factors, neonatal outcome and necessity for introducing national policy for intrapartum chemoprophylaxis. To evaluate the role of intrapartum chemoprophylaxis in preterm labor at <37 weeks of gestation, premature rupture of membranes at <37 weeks of gestation, fever during labor, ruptures of membranes >18 hours before delivery and previous delivery of a sibling with GBS disease. A total of 784 neonates admitted to the Neonatal Intensive Care Unit, from 1 January 2005 to 31 December 2005. 60 (10/1000 live born) developed early-onset infection (EOGBS). The dominant presentation for EOGBS was sepsis (65%), pneumonia (32.2%) and meningitis (3%). Mean gestational age was 34.5 (±5.3) weeks. There were 2 neonatal deaths (3%) in EOGBS, both preterm. EOGBS disease was associated with following risk factors: rupture of the membranes >12 hours (49.3%), chorioamnionitis (11.9%), status post cerclage (10.4%), diabetes mellitus (4.5%), delivery out of hospital (3%), uroinfection (1.5%). After AAP implementation the incidence of GBS infection decreased from 15/1000 to 10/1000 of live born infants. The mortality from EOGBS dropped from 5% to 3 %. The incidence of GBS infection in our study was considerably higher than in all current reports. Reasons for that can be inadequate perinatal screen in some parts of the country and no established policy for intrapartum antibiotic treatment of women with risk factors. Our results documented that intrapartum chemo-prophylaxis for GBS infection significantly reduces perinatal mortality due to neonatal infection and sepsis.

***Key words**: Group B streptococcus infection, neonatal outcome, prophylaxis, prevention*

Introduction

Colonization with group B beta-hemolytic streptococci (GBS) at any time during pregnancy is an important risk factor for neonatal sepsis and it has long been recognized as a frequent cause of morbidity in parturient women, and of mortality and morbidity in the newborn infants[1]. Early onset group B streptococcal infection (EOGBS) is one of the major neonatal infections in developing countries but also in industrialized ones[2]. The clinical features for EOGBS and LOGBS (Late onset of group B neonatal infection) disease are summarized in Table 1.

In many countries, in particular in US, several recommendations have been proposed to prevent the perinatal GBS infection[4]. The most important problem in the prevention programme is the identification of the cases to treat, since it is not possible to give antibiotics to all the women. In 1996, the federal Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) recommended an approach for prevention of early onset GBS infection in neonates based on risk factors. These strategies, either a risk-based or a culture-based program, have been responsible for reduced incidence of GBS newborn disease from 1.7 to 0.4/1000 live births in the years 1993 to 1999 in the United States[5]. In Croatia we combine two strategies for

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TABLE 1
COMPARISON OF EARLY ONSET GROUP B STREPTOCOCCAL INFECTION AND LATE ONSET GROUP B STREPTOCOCCAL INFECTION

Feature	EOGBS	LOGBS
Age range	<7 days	7 days–3 months
Median age at onset	1 hour	27 days
Maternal complication	Common	Uncommon
Incidence of prematurity	Frequent (30%)	Uncommon
Mortality rate	5–20%*	2–6%

*<10% in term infants (modified with permission from Baker, C. J., N. A. Halsey, A. Schuchat, AAP Modified guidelines for prevention of early-onset group B streptococcal disease. Pediatrics., 103 (1999) 71)[3]

the identification of the women to be treated, one risk based and the other screening based[6]. The incidence of EOGBS infection in Croatia before the implementation of the Protocol was much higher than in most of the studies (15/1000 live births; mortality rate 5%), so we believed that intrapartum chemoprophylaxis in risk patients can reduce the mortality and consequences of GBS infection in newborns[2,6].

The aim of our study was to compare the newborn infection rate with GBS before and after the introduction of AAP protocol. Other objective was to evaluate the prevalence of antenatal risk factors and mortality rates in high risk obstetrical patients, and to propose the introduction of intrapartum chemo-prophylaxis as a part of our national policy.

Patients and Methods

A prospective study of all newborn babies admitted to the Neonatal Intensive Care Unit (NICU) at Department of Obstetrics and Gynecology, School of Medicine, University of Zagreb, for the year 2005 was analyzed to determine the incidence of GBS infection before and after AAP implementation in Croatia, antenatal risk factors and neonatal outcome.

Maternal screening for vaginal group B streptococci is not a routine and there is no written policy for intrapartum antibiotic treatment of high risk patients. Women who develop fever or who have prolonged rupture of membranes with chorioamnionitis often receive intrapartum antibiotics. There were 48 women in our study who received prophylaxis (2 g i.v. of Ampicillin initial dose and 1 g every four hours during the labour).

Surface swabs (skin) and gastric aspirat are taken from every newborn admitted to the NICU. Blood culture from the umbilical cord also collected at the time of delivery in a delivery room from any baby born to a mother with a fever or if the membranes have been ruptured for over 16 hours. Swabs and blood culture are plated on to blood agar and incubated in 5 % CO_2. If beta haemolytic colonies are penicilin sensitive they are serotyped to confirm group B streptococci.

Definite early onset group B streptococcal infection was defined as a positive blood and/or cerebrospinal fluid culture in the context of clinical sepsis in a baby aged less than 48 hours. Probable EOGBS infection was defined as clinical signs consistent with EOGBS infection in a baby under 48 hours old, colonized with group B streptococci[7].

Definition of definite Early Onset Group B Streptococcal disease

Sepsis: a pure growth of group streptococci from one or more blood culture bottles associated with clinical sepsis. Meningitis: a pre growth of group B streptococci from cerebrospinal fluid or pleocystosis and positive blood cultures. Pneumonia: respiratory distress cosistent with pneumonia and the radiographic appearance of streaky opacities or confluent lobar opacification persisting for more than 24 hours, in addition to a positive blood culture for group B streptococci.

Definition of probable Early Onset Group B Streptococcal disease

All infants had significant laboratory findings for infection (high CRP, more than 10% bands in peripheral blood picture/left shift or thrombocytopenia) and one of the following: Probable group B streptococcal pneumonia: respiratory distress consistent with pneumonia and the radiographic appearance of streaky densities or confluent lobar opacification persisting for more than 24 hours, in an infant colonized with group B streptococci. Probable group B streptococcal sepsis: an infant colonized with group B streptococci in the presence of two of the following clinical sings: respiratory deteration, thrombocytopenia, bowel stasis or poor perfusion/ hypotension.

For statistical analyses, we used chi-square test, Student's t-test and Mann Whitney test. We considered $P<0.05$ to be statistically significant.

Results

During the period between 1 January 2005 and 31 December 2005 there were 784 infants admitted at the NICU. All results are shown in the tables.

From that number 152 (19.4%) infants had clear clinical signs of early onset infection in first 24 hours of life. The newborn infection rate with EOGBS infection was significantly lower after the introduction of AAP protocol ($p=0.0013$).

Sixty seven neonates had EOGBS disease, 60 (90%) positive cultures (definitive infection), and 7 (10%) probable infection. The incidence of definite EOGBS infection was 10 per 1000 live births and the incidence of probable infection was 2 per 1000 live births.

After year 2000 and intrapartum chemoprophylaxis the incidence of GBS decreased to 10/1000 live born infants and the mortality dropped to 3% with increased incidence of Gram negative microorganisms and decreased incidence of Gram positive.

TABLE 2
ADMISSION RATE IN NEONATAL INTENSIVE CARE UNIT AND THE INCIDENCE OF EARLY ONSET GROUP B STREPTOCOCCAL INFECTION

Year	Birth rate (N)	NICU (N)	%	Clear signs of EOGBS	%
1999	4817	761	15.8	201	26.4
2005	4130	784	18.9	152	19.4
p			NS		0.0013

NICU – Neonatal Intensive Care Unit; EOGBS – Early Onset Group B Streptococcal Infection

TABLE 3
COMPARISON OF THE MOST COMMON ISOLATES IN EARLY ONSET GROUP B STREPTOCOCCAL INFECTION IN COMPARED PERIOD

Isolates (%)	Year 1999	Year 2005	p
GBS	59.8	44.1	P=0.0000
E. coli	29.8	40.1	P=0.0000
Enterococcus	7.6	11.2	P=0.156
Candida	1.3	2.6	P=0.065
Pseudomonas	1.5	0.7	P=0.1309

GBS – Group B Streptococcus

TABLE 4
DOMINANT PRESENTATION OF EARLY ONSET GROUP B STREPTOCOCCAL INFECTION IN COMPARED PERIOD

Presentation	Year 1999 (%)	Year 2005 (%)	p
Sepsis	63	65	NS
Pneumonia	36	32.2	NS
Meningitis	1	3	NS

The dominant presentation for definite EOGBS disease was sepsis with an increased incidence of meningitis. Of 7 neonates with probable infection, 4 (57.2%) had sepsis, and 3 (42.9%) had pneumonia.

Table 5 shows the most common risk factors for EOGBS. We found decreased incidence in status post cerclage ($p<0.05$) and delivery out of the hospital ($p<0.05$) in compared years.Twelve neonates were not considered at high risk for EOGBS infection.

Ten neonates with EOGBS disease were on the artificial ventilation, the average duration of ventilation was 12 days. The gestational age of definite cases varied from 28 to 42 weeks, with a mean (SD) of 34.5 (±5.3) weeks. 28 (46.7%) of 60 neonates with definite EOGBS infection were preterm (<37 weeks gestation). The mean gestational age of babies with probable EOGBS infection was 36.5 (±5.2) weeks. The rate of neonates small for ages in group with EOGBS infection was 83.5 %. Two (3%) neonatal deaths were attributed to EOGBS infection, and all of them were neonates with definite infection. Two neonates who died were both preterm and their gestational ages were 28 and 33 weeks. GBS was found in cervical smears in 7 of 67 mothers (10%) of neonates with EOGBS disease.

TABLE 5
THE INCIDENCE OF DOMINANT RISK FACTORS FOR EARLY ONSET GROUP B STREPTOCOCCAL INFECTION IN COMPARED PERIOD

Risk factors	Year 1999 (%)	Year 2005 (%)	p
RVP ≥ 12 hours	46.6	49.3	NS
Chorioamnionitis	10.7	11.9	NS
Status post cerclage	15.2	10.4	NS
Diabetes mellitus	4.1	4.5	NS
Delivery out of hospital	5.3	3.0	NS
Uroinfectio in pregnancy	1.3	1.5	NS

RVP – Premature rupture of membranes

Discussion

In Croatia, before year 2000, when we started with AAP guidelines, the incidence of GBS was 15/1000 live born infants, and mortality from EOGBS was 5%[2]. After year 2000 and intrapartum chemoprophylaxis the incidence of GBS decreased to 10/1000 live born infants, and the mortality rate dropped to 3% with increase incidence of Gram negative microorganisms and decrease incidence of Gram positive (Table 3). Our data suggest that the incidence of EOGBS infection in our institution (10/1000 live births) is still higher than in most other reports (0.4–5/1000 live births)[8]. In the field of perinatal medicine there was an evident increase of GBS infection[9]. The first cases of human infection with GBS were reported in the 1930s. This organism was virtually unknown to the clinicians until 1964, when the first study of perinatal GBS infections was published[10]. By the 1970's, GBS emerged dramatically as the leading cause of maternal and neonatal infection with fatality rates of 20–50%[11]. In the pre-prevention era active surveillance for invasive neonatal GBS disease estimated that approximately 6,100 early-onset cases and 1,400 late-onset cases occur annually in the United States[12]. In 1996, the first national consensus guidelines were released. Since then, there has been a 70% reduction in early-onset neonatal GBS infection, but no decrease in late-onset neonatal GBS disease[13]. In 2002, new AAP guidelines were introduced recommending: 1) solely screen based prevention strategy, 2) new algorithm for patients with penicillin allergy and 3) more specific practices in certain clinical scenarios[14]. After prevention implementation incidence of GBS infection declined by 70% to a rate of 0.5/1000 live births in the United States[15].Regarding the literature, pregnancy itself does not influence colonization rates[16]. Maternal colonization rates in the United States are 26%[17]. Regarding our data GBS was found in cervical

smears in 7 of 67 mothers (10%) of neonates with EOGBS disease. Neonatal GBS incidence date for Europe have been reported only from the Netherlands (1.9/1000 live births), England (0.72/1000 live births) and Germany (0.47/1000 live births)[18].

In our research we confirmed our hypothesis in decreasing the incidence and the mortality rate of EOGBS in newborns after introducing intrapartum chemo-prophylaxis in risk pregnancies (Table 2), but we are still not satisfied. Reasons for that can be in our definition of EOGBS infection[3], higher rate of rectovaginal GBS carriage of pregnant women in Croatia, no consistent policy for intrapartum antibiotic treatment of women with risk factors, poor perinatal screening in some parts of the country and differences in ethnic or specifically genetic factors between the population in Croatia and in the United States and western European countries.

The prevalence of risk based strategy of identifying candidates for treatment may be more effective. Our results shows that more than 80% of women who delivered neonates with EOGBS disease had one of the risk factors from AAP guidelines, but we noticed two more which we did not find in other studies (status post cerclage 10.4% and delivery out of the hospital 3%). We also found their decreasing incidence after introducing the Protocole (Table 5), but without statistically importance.

More then 90% of EOGBS disease and almost all fatal infections occur within the first day of life, with a median age at onset of 1 hour[8]. The dominant presentation for EOGBS disease in our study before and after chemoprophylaxis is sepsis (63% vs. 65%) with or without of respiratory distress (RDS) and pneumonia (36% vs. 32.2%). Meningitis occurs in an estimated 5% to 10% of EOGBS cases in the literature and 1% and 3% in our study[19] (Table 4). Antibiotic therapy (Penicillin and Garamycin) was immediately introduced to all our infants with clear clinical signs of early onset infection. After 48 hours, antibiotic therapy was modified according to the result of an antibiogram. Infection caused by GBS was treated with penicillin, caused by E. coli was treated with Garamycin, caused by Enterococcus was treated by Ampicillin, caused by Candida was treated by Diflucan, and caused by Pseudomonas was treated by Cefepim. Fatal infection is associated commonly with fulminant and overwhelming EOGBS disease and with the irreversible consequences of LOGBS infection. From the data in the literature, the birth weight-specific mortality for infants with bacteriemia remains increased 25–30% for neonates weighing less than 2.5 kg and 2–4% for neonates more than 2.5 kg[20]. The mortality rate according our results decreased from 5% in 1999 to 3% in 2005 all due to prematurity.

Despite identification of intrapartum chemoprophylaxis as an effective intervention, controversy continued to surround prevention methods of identifying candidates for chemoprophylaxis[21]. Competing strategies included: 1) monitoring women for known obstetric risk factors (fever, preterm labor, prolonged membrane rupture) during labor and 2) performing culture-based screening of women before labor and to identify women colonized with GBS. Screening proponents also disagreed about the best time to perform screening[22].

Either prenatal GBS screening or a risk-based strategy could potentially prevent a substantial portion of GBS cases[22]. In selecting the patients who should receive intrapartum prophylaxis, recent data suggested that screening programs for the detection of GBS prevalence may be more effective than risk- based strategies for prevention of EOGBS. Combined vaginal and rectal swabs, collected between 35 and 37 weeks gestation provide optimum conditions to detect presence of the infection[18]. Sepsis caused by other organisms is more often a disease of prematurity[19]. Intrapartum antibiotic prophylaxis seemes to be efficient against the EOGBS sepsis by interrupting vertical GBS transmission and it is now a largely preventable public health problem[20].

It seems important to develop and implement Croatian national prevention policy for prevention and treatment of peripartal GBS infection. Studies indicate that intrapartal prophylaxis of GBS carriers and selective administration of antibiotics to the newborns may reduce neonatal GBS sepsis to a level of 80–95%[11]. Interruption of GBS vertical transmission is dependent upon maternal treatment before fetal colonization. Intrapartum chemoprophylaxis must be selected based on maternal allergy history and susceptibility of GBS isolates[23]. Intravenous penicillin G is the preferred antibiotic, with ampicillin as an alternative. Penicillin G should be administered at least four hours before delivery for maximum effectiveness. Cefazolin is recommended in women allergic to penicillin who are at low risk of anaphylaxis. Clindamycin and erythromycin are options for women at high risk for anaphylaxis, and vancomycin should be used in women allergic to penicillin and whose cultures indicate resistance to clindamycin and erithromycin or when suspectibility is unknown. However, the severity of ampicillin-resistant E. coli sepsis and its occurrence after maternal antibiotics suggest caution regarding the use of ampicillin instead of penicillin for GBS prophylaxis[21]. A written protocol for prevention of GBS infection in newborn must be adopted in every delivery centre.

The population reported in our study may not be typical of the entire Croatian population, and it is likely that the incidence of GBS infection is different in other parts of Croatia. Studies on the incidence in different regions are needed to establish a basis for trials on different strategies to reduce EOGBS infection.

Continued efforts to eradicate GBS newborn disease require an early detection of the pathogen, better understanding of the colonization and transmission, implementation of effective sampling techniques and therapy.

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MATERNALNA INFEKCIJA HEMOLITIČKIM STREPTOKOKOM GRUPE B, NEONATALNI ISHOD I ULOGA POSTUPAKA PREVENCIJE

SAŽETAK

Kolonizacija beta hemolitičkim streptokokom iz grupe B tijekom trudnoće ubraja se u visoko rizični čimbenik za neonatalni morbiditet i mortalitet, a u zemljama u razvoju vodeći je uzrok neonatalne infekcije i teške neonatalne sepse. Posljedično tome, 2000. godine uveli smo Protokol za prevenciju perinatalne infekcije beta hemolitičkim streptokokom i u ovom istraživanju analizirali rizične čimbenike za nastanak infekcije, učestalost novorođenačke infekcije beta hemolitičkim streptokokom grupe B prije i nakon uvođenja Protokola te neonatalni ishod u uspoređivanim razdobljima. Utvrdili smo da je uvođenjem Protokola učestalost novorođenačke infekcije pala s 15/1000 živorođene djece na 10/1000 živorođene djece, a mortalitet s 5 na 3%. Dominantna klinička slika u infekciji novorođenčadi beta hemolitičkim streptokokom u promatranim razdobljima je sepsa.Najčešći rizični čimbenici za nastanak novorođenačke infekcije bili su prijevremeno prsnuće membrana (49,3%) te korioamnionitis (11,9%). Učestalost neonatalne infekcije beta hemolitičkim streptokokom nakon uvođenja Protokola u našem se istraživanju pokazala i dalje visokom u usporedbi s podacima iz literature. Uzroci mogu biti u neadekvatnom probiru pacijentica te nedostatku odredbe za obaveznu intrapartalnu kemoprofilaksu rodilja s rizičnim čimbenicima.