Prevention of Early-Onset Neonatal Group B Streptococcal Infection: is Universal Screening by Culture Universally Applicable?

Vered H. Eisenberg MD MHA[1]*, David Raveh MD[2], Yair Meislish MD[3], Bernard Rudensky PhD[4]*, Yossef Ezra MD[1], Arnon Samueloff MD[1], Arthur I. Eidelman MD[3,5] and Michael S. Schimmel MD[3]

Departments of [1]Obstetrics and Gynecology, [2]Infectious Diseases, [3]Neonatology and [4]Clinical Microbiology, Shaare Zedek Medical Center, Jerusalem, Israel
Affiliated to Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[5]Affiliated to Faculty of Medicine, Hebrew University-Hadassah Medical School, Jerusalem, Israel

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Abstract

Background: Previous assessments of maternal group B Streptococcus carrier rates in women delivering at Shaare Zedek Medical Center ranged between 3.5 and 11% with neonatal sepsis rates of 0.2–0.9/1000 live births. Because of low colonization and disease rates, routine prenatal cultures of GBS were not recommended and intrapartum prophylaxis was mainly based on maternal risk factors.

Objectives: To determine whether this policy is still applicable.

Methods: We performed prospective sampling and follow-up of women admitted for labor and delivery between February 2002 and July 2002. Vaginal and rectal cultures were obtained before the first pelvic examination. GBS isolation was performed using selective broth medium and identified by latex agglutination and serotyping. Demographic data were collected by means of a standardized questionnaire. Data on the newborns were collected throughout 2002.

Results: Of the 629 sampled women, 86 had a positive culture and a carrier rate of 13.7%. A borderline significantly higher carriage rate was observed among mothers of North American origin (21% vs. 13.1%, $P = 0.048$), and a higher attack rate in their infants (3.8/1000 compared with 0.5/1000 live births in our general maternal population, $P = 0.002$). Eight newborns had early-onset neonatal GBS sepsis (a rate of 0.8/1000 live births), but none of them benefited from intrapartum antibiotic prophylaxis.

Conclusions: An increased neonatal disease rate was observed in a population with a higher colonization rate than previously seen. In view of the higher carrier rates, we now recommend routine prenatal screening for GBS in our perinatal population.

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Group B streptococcal infection is the leading cause of life-threatening disease in the early neonatal period. Maternal GBS colonization rates vary between 3% and 40% [1]. In the absence of antibiotic treatment, approximately 50% of infants delivered from colonized women become colonized at birth [1]. Approximately 1 of every 75 colonized infants develops early-onset GBS disease and 25–30% of cases occur in preterm infants [1]. The incidence in the United States is persistently about 1.2/1000 live births [1]. The rate of GBS disease in the absence of a prevention strategy is reported to be 1.5–2.0 cases per 1000 live births [2].

Various preventive regimens have been recommended by several authorities, the most recent being the revised Centers for Disease Control guidelines [2], which were later endorsed by the American College of Obstetricians and Gynecologists and by the American Academy of Pediatrics. These guidelines advocate the implementation of universal GBS culture screening at 35–37 weeks gestation and administration of intrapartum antibiotic prophylaxis to mothers found positive on screening. Women who were not screened receive intrapartum antibiotics according to the presence or absence of the following risk factors: labor before 37 completed weeks, maternal fever (≥ 38.0°C) during labor, prolonged rupture of membranes (≥ 18 hours), previous delivery of an infant with GBS disease, and GBS urinary tract infection during pregnancy. Maternal colonization with GBS in the absence of identifiable risk factors may account for 25–30% of infants with early-onset disease.

The implementation of prevention strategies has indeed resulted in a decreased incidence of GBS disease. The use of intrapartum prophylaxis with antibiotics to prevent perinatal group B streptococcal infections has led to a 70% decline in the incidence of GBS disease in the past decade [2]. However, the variation in prevalence rates in different populations may actually preclude the implementation of uniform and universal guidelines. The question arises as to whether each population, and our own included, should accept the revised CDC guidelines as they appear, or whether modifications are in order.

Previous assessments of maternal GBS carrier rates in our obstetric population, which were performed in the years 1984, 1987, 1989, 1991 and 1997, ranged between 3.5 and 11%, with early-onset neonatal sepsis rates in the range of 0.2–0.9/1000 live births [3-5]. As a result of the low colonization and disease rates, routine prenatal cultures of GBS were not recommended, and intrapartum prophylaxis was mainly based on maternal risk factors. We performed an updated assessment of the carrier rate

* Dr. Eisenberg is currently at Sheba Medical Center, Tel Hashomer and Sackler Faculty of Medicine, Tel Aviv University; and Dr. Rudensky at Hadassah University Hospital and Hebrew University-Hadassah Medical School, Jerusalem, Israel.

GBS = group B Streptococcus

CDC = Centers for Disease Control

of GBS in our population in order to determine whether this policy is still applicable.

Patients and Methods

We screened women who were admitted for labor and delivery at the Shaare Zedek Medical Center in Jerusalem between 1 February 2002 and 31 July 2002. Our department targets a population of almost 10,000 deliveries per year. Neonatal GBS sepsis or meningitis was analyzed for the period between January and December 2002.

Vaginal and rectal cultures were obtained upon admission before the first pelvic examination. GBS was isolated using a selective broth medium (Todd-Hewitt) containing gentamicin, polymyxin, crystal violet and Tween, and identified by latex agglutination and antigen B assay. Antigen F served as the control. GBS-positive samples were sent for serotyping to the Central Ministry of Health Laboratory in Jerusalem. Women were prospectively followed throughout labor and delivery, the immediate postpartum hospitalization, and neonatal period.

The following parameters were recorded: maternal demographic characteristics, maternal origin (place of birth), maternal blood type, adequacy of prenatal care, presence or absence of previous screening for GBS, clinical risk factors during labor (gestation less than 37 completed weeks, membrane rupture longer than 12 hours before delivery, intrapartum temperature ≥ 38°C, GBS bacteriuria, and a previous infant with GBS disease), intrapartum antibiotic use, gestational age of the infant at birth (determined on the basis of the last menstrual period and/or ultrasound dating for corroboration), and the presence or absence of neonatal sepsis or meningitis. Intrapartum antibiotic prophylaxis was given to known GBS-positive women or in case of unknown or negative status according to risk factors. Risk factors were as stated above with one exception: antibiotic prophylaxis is given at our center after 12 hours of membrane rupture rather than 18 hours as recommended by the CDC and ACOG. (The statistical analysis is based on this fact.) The main outcome variables were neonatal early-onset GBS disease and maternal perinatal infection.

The institutional review board at our medical center approved the study protocol. The participating women granted verbal informed consent. None of the women who were asked to participate refused screening.

Statistical analysis

We applied the *t*-test, χ^2 test, and Fisher's exact test where required. $P = 0.05$ was considered statistically significant. Vital variables and variables with $P < 0.10$ were entered into the logistic regression models.

ACOG = American College of Obstetricians and Gynecologists

Results

During the study period 629 women were sampled from among 4650 deliveries. Of these, 86 had a positive culture for GBS, giving a carrier rate of 13.7%. Demographic characteristics of screen-positive versus screen-negative women are outlined in Table 1. Multivariate analysis revealed a significantly higher carrier rate among mothers of North American origin compared with mothers of other origins (21% vs. 13.1%, $P = 0.048$). The perinatal characteristics of screen-positive versus screen-negative women are given in Table 2. Two parameters reached significance on bivariate analysis. Gravidity as well as parity were significantly higher among screen-positive women ($P = 0.016$ and $P = 0.013$ respectively). There were no significant differences in multivariate analysis. GBS serotype 5 was found to be the most common serotype in our study population (full serotype data available on request).

Table 1. Demographic characteristics of the screen-positive versus screen-negative women

	Negative screen	Positive screen	Bivariate analysis	Multivariate analysis
All	543 (86.3%)	86 (13.7%)		
Ethnic group			NS	–
Jewish	505 (86%)	77 (14%)		
Non-Jewish	31 (82%)	7 (18%)		
Maternal age (yrs)	28.4 ± 6	29.04 ± 6	NS	–
Maternal country of birth			0.07	
Israel	401 (86%)	67 (14%)		NS
Eastern Europe	23 (88%)	3 (12%)		NS
Western Europe	43 (98%)	1(2%)		NS
Islamic countries	17 (89%)	2(11%)		NS
North America	37 (79%)	10 (21%)		=0.048
South America	11(91%)	1 (9%)		NS
Unknown	11 (85%)	2 (15%)		NS

Table 2. Perinatal characteristics of screen-positive versus screen-negative women

	Negative screen (n=543)	Positive screen (n=86)	Bivariate analysis	Multivariate analysis
Gravidity	3.855 ± 2.914	5.256 ± 5.423	0.016	NS
Parity	2.306 ± 2.344	3.141 ±2 .715	0.013	NS
Multiparity (> 6)	42 (8%)	10 (12%)	NS	
Previous uterine scar	29 (5%)	6 (7%)	NS	
Known GBS positive	4 (1%)	1 (1%)	NS	
Maternal diabetes mellitus	13 (2%)	4 (5%)	NS	
Maternal hypertension	12 (2.2%)	2 (2%)	NS	
White blood cell count at arrival (K/UL)	11.554 ± 2.94	11.08 7± 2.60	NS	
Length of membrane rupture (hrs)	5.576 ± 22.003	3.384 ± 5.471	NS	
Membrane rupture ≥ 12 hours before delivery	41 (7%)	21 (24%)	NS	
Delivery by cesarean section	5.3% (29/543)	7% (6/86)	NS	
Preterm delivery	20 (3.6%)	0		
Infant weight (g)	3275 ± 532	3344 ± 494	NS	
Apgar at 1 minute	8.89 ± 0.75	8.99 ± 0.11	NS	
Apgar at 5 minutes	8.95 ± 0.56	8.99 ± 0.12	NS	
No. of antibiotic doses	0.429 ± 2.206	0.288 ± 0.716	NS	

Table 3. Neonatal and perinatal characteristics of infants with neonatal sepsis

#	Maternal age (yrs	Gestational age (wks)	Country of origin	PROM (hrs)	Intrapartum antibiotics	Meningitis	Serotype	Outcome
1	25	41	NAM	2	No	No	Ia/c	Survived
2	21	40	NAM	3	No	No	NA	Survived
3	20	38	Other	6	No	No	III	Survived
4	21	39	Other	2	No	Yes	Ia	Survived
5	25	25	NAM	weeks	No	No	II	Died
6	23	38	Other	7.5	No	No	IIc/R	Survived
7	31	34	Other	21	Yes	No	/R	Survived
8	21	32	Other	0	Yes	No	NA	Survived

PROM = length of time of rupture of the membranes in hours, NA = not available, NAM = North American maternal origin

Table 4. Comparison between first and last GBS screening study performed at our institution

	1984	2002	*P*
Maternal colonization rate	5.4%	13.7%	0.00072 (95% CI 0.19–0.67)
Neonatal sepsis rate	0.2/1000	0.8/1000	< 0.01, OR = 4.26 (95% CI 0.13–0.39)
Most prevalent serotype	I	5	NA

CI = confidence interval, OR = odds ratio, NA = not applicable

Neonatal and perinatal characteristics of infants with early-onset GBS sepsis are given in Table 3. The overall early-onset GBS sepsis rate was 0.8/1000 live births. None of the eight newborns with early-onset infection benefited from intrapartum antibiotic prophylaxis. All mothers had an unknown GBS status upon admission. Five mothers presented without risk factors and therefore did not qualify for prophylactic antibiotics. Three mothers presented with premature labor; two of them received a single dose of antibiotics and delivered within less than 1 hour of arrival. The third arrived in active labor at 25 gestational weeks, reporting several weeks of suspected preterm premature rupture of the membranes for which she did not seek consultation. She delivered immediately; the neonate had severe GBS sepsis coupled with prematurity and died shortly after delivery.

A higher attack rate was observed in infants of mothers of North American origin (all Caucasians). Three of the eight infants with neonatal sepsis or meningitis were born to mothers of North American origin, constituting a rate of 3.8/1000 compared with 0.5/1000 live births in our general maternal population ($P = 0.002$).

A comparison between these results and our initial screening study in 1984 is presented in Table 4. We observed a significantly higher maternal colonization rate in the present study, 13.7% vs. 5.4% in 1984 ($P = 0.00072$); and a significantly higher neonatal sepsis rate, 0.8/1000 births in 2002 compared with 0.2/1000 in 1984 ($P < 0.01$). The most common serotype at the time of the 1984 study was type I.

The antibiotic sensitivity profile in our study showed 8% and 19% resistance to clindamycin and erythromycin, respectively.

Discussion

In the present study we observed an increase in the maternal GBS colonization rate and the early-onset GBS sepsis rate in comparison with previous assessments in our department. A specific subgroup that stands out with significantly higher colonization rates is the group of women who emigrated from North America. In this group, the rate was closer to the rates cited in the USA [1].

There are several drawbacks to this study. We screened for 6 months only because the screening protocol was difficult to implement due to an extremely busy delivery room at Shaare Zedek Medical Center. This is why we could not screen more women during the study period. Once we reached statistical power the study was discontinued. The neonatal analysis was performed over 12 months to comply with the common practice of the Israel Pediatric Society. During the actual study period there were seven cases of neonatal GBS. The last case occurred later during 2002. We believe that the explanation for the unusual attack rate during this period lies with the characteristics of the mothers of these newborns as elaborated in the results. The fact that none of these neonates benefited from intrapartum prophylaxis only serves to strengthen the recommendation for a screening-based approach because of the lack of risk factors during delivery. Those who did have risk factors (preterm delivery) were delivered within a short time, and therefore antibiotics were not given or were not sufficient.

It is also noteworthy that none of the eight newborns were born to women who were screened, which is another problem that hinders analysis. We do not have exact data regarding the length of stay in Israel of the women who reported being born in North America. The number of women of North American origin is small but there was statistical significance nonetheless. It seems that the carriage rate in these women resembles the carriage rates reported in the USA.

Despite these limitations, we believe that the results of our study are significant enough to merit close scrutiny. We now recommend universal GBS screening in the prenatal period in our maternal population. We decided not to limit the screening to women of North American origin, due to the overall increase in the carriage rate in our population. The revised CDC recommendations [2], which appeared near the time of the analysis of our data, only served to strengthen our belief. But, should the CDC recommendations be universally applied in all populations?

The implementation of a GBS screening-based approach has been shown to reduce the incidence of early-onset GBS sepsis by more than fivefold [6]. When compared with other prevention strategies, the screening-based approach was associated with the lowest estimated probability of early-onset sepsis but the highest total cost [7]. Rouse et al. [8] performed a decision analysis to understand the implications of 19 potential GBS infection prevention strategies. They found that a universal 36 week maternal culture, together with treatment of all patients experiencing preterm birth and of all culture-positive patients, resulted in a decrease to 14% of expected neonatal sepsis, with a 27% maternal treatment rate and low total costs. Intrapartum antibiotic prophylaxis was estimated to reduce the attack rate for early-onset GBS disease by 86% using the culture-based approach.

Yancey and colleagues [9] evaluated a comprehensive GBS treatment strategy involving over 800 women. They calculated the positive and negative predictive values of antenatal GBS cultures for populations with various colonization rates: for a lower colonization rate they noted a lower positive predictive value and a higher negative predictive value. For example, in a population with a carriage rate of 10%, the positive and negative predictive values are 71% and 99%, respectively. If, however, the carriage rate is 20%, the positive and negative predictive values are 85% and 97%, respectively.

According to the CDC, institutions using antepartum screening had fewer cases of early-onset GBS sepsis, namely more cases of GBS could be prevented by the implementation of the culture-based approach. However, this would be invalid in a population that does not have prenatal care [2]. Main and Slagle [10] compared the risk factor-based approach with the culture-based approach in a tertiary care hospital and found that the culture-based protocol significantly reduced early-onset GBS infection without increasing infections from resistant organisms. (However, the literature is not conclusive on the issue of neonatal sepsis secondary to an antibiotic-resistant microorganism.) The authors state that the optimal approach to GBS chemoprophylaxis is not uniform and may vary among different sites, according to the local frequency of early-onset GBS infection, frequencies of other early-onset bacterial infections, the organization of medical care, and the patient population. Since the rate of GBS carriage in our population is similar to the one cited in their study, we felt it advisable to accept their recommendations.

Universal screening increases the cost of perinatal care. The cost-effectiveness of the various treatment protocols for GBS prevention was investigated by Strickland et al. [11], and by Boyer [12]. The authors suggested that because of the high cost of caring for neonates with early-onset disease, screening and treatment is justified from both a medical and an economic standpoint. However, based on their calculations, they state that in geographic areas where the maternal GBS colonization rate is less than 10%, universal screening programs are not cost-efficient. Therefore, according to Strickland and co-authors [11], only if the carrier rate in a population is higher than 10% is it appropriate to perform universal screening.

On the other hand, Fargason and his team [13] found that the culture-based approach is associated with greater pediatric costs for the management of asymptomatic full-term infants compared with the risk factor-based approach, when considering the cost per case of sepsis, which can be prevented. In populations with a very low GBS attack rate, the estimated cost per case prevented would be correspondingly less favorable using the screening-based approach. At higher maternal carriage rates there is a greater percentage reduction in sepsis and cost using the culture-based approach. The authors conclude that regional variability in the rates of colonization and of early-onset disease may require careful scrutiny when selecting a prevention strategy.

There are varied reports concerning the GBS carriage rate worldwide outside the USA. These range from 4.4% to 32.9% [14-20]. One study from southern Israel reported a rate of 12.3%, with the carriage higher in immigrants from the former Soviet Union [16]. Trijbels-Smeulders et al, [21] reported the results of data collected from a questionnaire concerning GBS, which was sent to members of the European Society for Pediatric Infectious Disease and European Association of Perinatal Medicine. Despite a low 15% response rate, the data collected by them showed that in most European countries the incidence of GBS colonization among pregnant women varies between 10 and 20% and the incidence of early-onset neonatal GBS infection ranges from 0.5 to 2 per 1000 live births. Nationwide prevention guidelines at the time of the report existed in only a few European countries, such as Denmark, Netherlands, Norway and Spain. Of these, only Spain has adopted a screening-based approach. They conclude that a surveillance study in European countries is needed to determine the most appropriate prevention policy.

The variation in carriage rates of maternal GBS and in attack rates in their infants could be related to the local distribution of GBS serotypes. Indeed, in our study population the most common serotype was serotype V. Type V is reported to be more frequent in the eastern region of the USA (New York and New Jersey) [22], which is where most Americans who emigrated to Israel came from. The recent shift in serotype prevalence has been speculated to be the cause of changes in GBS maternal and neonatal epidemiologic factors [23]. Our study population is a good example of this shift, and raises the question whether the emergence of serotype V is responsible for high colonization and attack rates.

The choice of a prevention strategy should be based on the rate of GBS carriage in a population, the neonatal GBS sepsis attack rate in that population, and the availability of the resources required to carry out the preferred strategy. Universal maternal GBS screening has been shown to be the most efficient strategy for prevention of neonatal GBS disease [2]. In countries or in populations where the local rate exceeds 10%, universal screening also becomes cost-effective, and is therefore strongly recommended [11]. However, increased exposure to intrapartum antibiotic prophylaxis in the era of maternal screening has been associated with late-onset serious bacterial infections in the infants [24]. Regional variations in GBS carriage rates in the same country may occur. Furthermore, ascertainment of the serotype distribution should be part of the decision-making process. When colonization rates are below 10% universal screening is not cost-effective, and decision analysis should take into consideration various factors specific to the population in question. Until a vaccine is developed it is imperative to maintain a valid and effective GBS prevention strategy. We believe that each country should conduct a periodic assessment of its local rate of GBS colonization, even if traditionally low maternal GBS colonization rates have been observed. A decision analysis should follow for each population in order to facilitate the choice of protocol and its implementation.

A recent excellent review on GBS [25] also discussed the lack of updated information on the status of GBS carriage in Israel. Our study along with the study from the south of Israel [16] provides new information on the carrier rate in our country. Both

studies highlighted a specific population with a higher carriage rate – women from North America and women from the former USSR, respectively. One can argue that both study populations are unique, which they are, but together they constitute roughly 15–20% of the Israeli population. Therefore, even if we assume that only in parts of the country does the carrier rate exceed 10%, this knowledge raises the question whether the current prevention strategy is sufficient or whether it merits reassessment. We believe, based on our findings, that a universal screening culture should be considered in Israel. We suggest that a national surveillance study be performed to validate this approach.

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Correspondence: Dr. V.H. Eisenberg, P.O. Box 526, Shoham 73142, Israel.
Phone: (972-3) 979-9955
Fax: (050) 681-1171
email: veredeis@post.tau.ac.il