Maternal Antibody at Delivery Protects Neonates From Early Onset Group B Streptococcal Disease

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Background. Further reduction in the group B streptococcal (GBS) disease burden in neonates in the United States awaits an additional prevention strategy, such as maternal immunization.

Methods. We performed a prospective, multicenter, case-control study of 33 mothers delivering neonates with early onset GBS infection (cases), and 99 age- and ethnicity-matched mothers colonized with the same capsular polysaccharide (CPS) types delivering healthy neonates (controls). Relative risk and absolute risk were calculated for early onset disease associated with concentrations of type Ia, III, or V CPS-specific antibody in maternal serum.

Results. For GBS types Ia and III, maternal CPS–specific antibody concentrations of ≥0.5 µg/mL were associated with a relative risk of approximately 0.1 (95% confidence intervals [CIs], .01–.74 and 0–.72, respectively; $P = .02$ for each), corresponding to a 90% risk reduction (by logistic regression). For type V, the relative risk was 0.3 (95% CI, .01–3.1), corresponding to a 70% risk reduction. By Bayesian modeling, the risk of early onset disease would decrease by 70% if maternal CPS-specific antibody concentrations for these 3 GBS types were ≥1 µg/mL.

Conclusions. Maternal CPS-specific antibody serum concentrations of ≥1 µg/mL at the time of delivery appear to protect most neonates from early onset GBS type Ia and III disease.

Keywords. Group B *Streptococcus*; neonate; neonatal sepsis; meningitis; glycoconjugate vaccine; immunization; serocorrelate; protective immunity.

Invasive group B streptococcal (GBS) infection emerged in the 1970s as a dominant cause of morbidity and mortality in neonates [1] and continues to be the single most frequent cause of neonatal septicemia and meningitis in the United States [2]. A correlation between a low concentration of maternally derived antibody against the capsular polysaccharide (CPS) of type III group B *Streptococcus* and infant susceptibility to GBS type III infection was described in the mid-1970s [3, 4]. Such an association also was demonstrated for neonatal infections caused by other GBS types [5, 6]. This association, in part, explains the discrepancy

between high rates of neonatal exposure to maternal colonization during labor and delivery (approximately 25%–30%) and the low incidence of early onset disease (approximately 1–3 cases per 1000 live births or approximately 1% of exposed) [7]. Meanwhile, the incidence of early onset disease has been reduced since the Centers for Disease Control and Prevention issued consensus recommendations with several professional organizations in 2002 for universal GBS culture screening of all pregnant women and intrapartum antibiotic prophylaxis for all GBS carriers [7]. By 2011, the incidence of early onset GBS disease had fallen to 0.25 cases per 1000 live births, representing a >80% reduction in incidence since 1993. However, the incidence has not been substantially decreased since 2007, suggesting that additional prevention methods should be developed [8].

Investigational GBS capsular polysaccharide–protein conjugate vaccines for 5 CPS types causing >95% of invasive disease, Ia, Ib, II, III, and V [8], were designed and evaluated in clinical trials in the 1990s. In healthy,

nonpregnant adults, these GBS glycoconjugate vaccines were well tolerated, significantly more immunogenic than the uncoupled CPSs, and elicited antibodies predominantly of the immunoglobulin G (IgG) isotype that promoted opsonophagocytic killing of homologous GBS types in vitro [9–12]. A candidate GBS trivalent Ia, Ib, and III glycoconjugate vaccine currently is undergoing phase II clinical trials in pregnant women (ClinicalTrials.gov identifier: NCT01446289). As this or perhaps other GBS vaccines are being developed, it is important to define the concentration of maternal antibodies against the individual CPSs of GBS at delivery that correlates with passive protection against invasive neonatal infection. Such a quantitative serologic correlate of protective immunity has been established for licensed polysaccharide-protein conjugate vaccines that prevent infant and childhood infections caused by *Haemophilus influenzae* type b and *Streptococcus pneumoniae* [13, 14].

We compared the concentrations of naturally acquired GBS CPS Ia-, III-, and V-specific IgG in sera of women giving birth to neonates who developed early onset (at <7 days of age) GBS disease to concentrations in sera of GBS Ia–, III–, or V–colonized mothers during labor and who delivered infants who remained well. Statistical methods were used to define the concentrations of CPS-specific antibody in maternal sera that conferred protection against early onset neonatal GBS disease caused by CPS types Ia, III, and V.

METHODS

Participants, Setting, and Procedures for Case-Control Study

This was a matched case-control study performed before widespread implementation of antenatal GBS screening and intrapartum antibiotic prophylaxis (1998–1999). Cases of early onset disease caused by type Ia, III, or V GBS were identified by prospective, multicenter, laboratory-based surveillance for invasive early onset GBS disease conducted in 6 hospitals in Houston, Pittsburgh, and Seattle [15]. Study personnel communicated at least once per week with 6 hospital microbiology laboratories in the 3 cities. Invasive infection was defined as isolation of GBS from a normally sterile site (blood or cerebrospinal fluid) in an infant <7 days of age. When a case was identified, study personnel determined whether a hospital admission blood sample was available from the infant's mother. If so, this was transported to an investigator's laboratory and centrifuged for separation of serum, which was then frozen at −80°C until testing. Among cases caused by the GBS types Ia, III, and V, 33 had maternal delivery sera available for study.

Three controls were matched to each case by 2 demographic factors known to increase likelihood of early onset disease, maternal ethnicity (white, black, non-black Hispanic, Asian, or other) and age, and by maternal colonization with the same GBS CPS type as that causing illness in the case mother's infant (ie, neonatal exposure to this potential pathogen). No attempt

was made to match for other risk factors known to increase the risk for early onset GBS disease, specifically chorioamnionitis, rupture of membranes ≥18 hours or delivery at <37 weeks' gestation. These control women were identified through 2 investigations undertaken during the same interval [15, 16], and all had delivery sera available for testing. These studies were approved by the institutional review boards for human research at each of the investigator's institutions and hospitals.

Specimen Collection and Laboratory Methods

Lower vaginal and rectal swab specimens from maternal controls were collected for culture at hospital admission for delivery, using the CultureSwab Transport System (Difco, West Molesey, Surry, UK), and processed for identification of GBS in the investigators' laboratories. Invasive disease isolates and available maternal sera were obtained from the hospital laboratories of each case. Invasive and colonizing GBS isolates had CPS type determined by a previously described method [17].

Types Ia, III, or V CPS–specific antibody in serum samples was measured by enzyme-linked immunosorbent assays (ELISAs). The quantitative determination of types Ia, III, and V capsular polysaccharide–specific IgG by ELISAs has been detailed previously [9, 12, 18]. The lower limits of detection for the type Ia, III, and V ELISAs were 0.05, 0.05, and 0.012 μg/mL, respectively; when required, these were accommodated in statistical analysis by use of censored data methods.

Statistical Analysis

The Fisher exact test was used for comparison of cases and controls by demographic characteristics and obstetrical factors. CPS-specific IgG concentration distributions for cases and controls were summarized nonparametrically [19] and by Weibull models [20]. Exact conditional logistic regression [21] was used with the matched case-control sets to estimate relative risks of early onset neonatal disease by concentration of maternal IgG to type Ia, III, or V GBS.

Quantitative appraisal of the absolute infant disease risk associated with various type-specific antibody concentrations in maternal sera was conducted in a Bayesian framework [22]. We used the Bayesian framework to obtain formal probability statements on the relationship between antibody level and disease risk in the presence of epidemiological uncertainty. The absolute disease risk of GBS type-specific IgG concentration, c, was defined as the probability that a woman colonized with type Ia, III, or V GBS and with a type Ia, III, or V-specific antibody concentration c or greater would give birth to a neonate who would develop early onset GBS disease caused by that GBS type. This probability, denoted $Pr(D|Ab \geq c)$, was calculated for a range of values of c, using a $\beta(25,2500)$ prior distribution on the marginal probability of disease, $Pr(D)$. $\beta(25,2500)$ means that the central 95% of the prior distribution of marginal risk lies between 0.64% and 1.41%. This model for the unconditional

Table 1. Characteristics of Mothers Delivering Neonates With Early Onset Disease and Control Mothers Colonized With Group B Streptococci at Delivery Delivering Healthy Neonates

| | Capsular Polysaccharide Type | | | | | |
| | Ia | | III | | V | |
Characteristic	Cases (n=17)	Controls (n=51)	Cases (n=9)	Controls (n=27)	Cases (n=7)	Controls (n=21)
Age, y, median (IQR)	24 (22–28)	24 (22–28)	20 (19–35)	22 (19–30)	29 (24–31)	28 (25–31)
Ethnic origin						
White, non-Hispanic	4	15	1	3	2	11
Black, non-Hispanic	3	9	2	6	0	0
Hispanic	9	24	6	18	4	9
Asian	1	3	0	0	0	0
Other	0	0	0	0	1	1

Data are no. of subjects, unless otherwise indicated.

Abbreviation: IQR, interquartile range.

risk of disease, independent of specific IgG concentration, implies a most likely value of overall risk of invasive disease among neonates born to colonized women of approximately 1% [23]. Uncertainty in Pr(D|Ab ≥ c) was evaluated using standard formulas [20, 22] and computer-intensive Bayesian modeling described elsewhere [22, 24]. The most likely value, or posterior mode, of Pr(D|Ab ≥ c), given the data, is referred to as the predicted absolute risk of disease [22]. Sensitivity analyses were conducted to verify that inferences on absolute risk were qualitatively robust [22].

RESULTS

Participant Characteristics

Thirty-three women were identified whose neonates developed early onset GBS invasive infection caused by CPS types Ia, III, or V. Seventeen infections were caused by type Ia, 9 by type III, and 7 by type V GBS strains. Each of the 33 infants had bacteremia, and 4 (3 with type Ia and 1 with type III) also had meningitis. The demographic characteristics of case mothers and of control mothers with vaginal and/or rectal GBS colonization at delivery but unaffected infants are shown in Table 1. Neonates with type III disease tended to be born to slightly younger women, but the interquartile range in age was broad for cases and their controls. In 3 instances, it was not possible to match cases with controls for age and ethnicity; thus, 2 Hispanic case mothers and 1 case mother of other ethnicity were matched to white controls.

Case mothers were significantly more likely than controls to have factors predisposing to risk for neonatal GBS infection, including a temperature of ≥100.4°C before delivery (24% vs 7%; $P < .01$) or chorioamnionitis (30% vs 1%; $P ≤ .001$). Case mothers also were more likely than controls to have preexisting or gestational diabetes mellitus (18% vs 1%, excluding 11 controls for whom diabetes mellitus status was not specified; $P = .$

002). Case mothers were not significantly more likely than controls to have rupture of membranes for ≥18 hours before delivery (9% vs 4%; $P = .37$) or to deliver an infant of <37 weeks' gestation (12% vs 11%; $P = 1.00$). With regard to delivery before 28 weeks' gestation, when maternal antibodies would be unlikely to be protective against neonatal exposure to GBS, no case infant but 3 control infants had this very early gestation and a birth weight of <1500 g. The similarity in frequency among cases and controls in prolonged rupture of membranes and delivery before 37 weeks' gestation, 2 of 4 maternal risk factors associated with enhanced risk for early onset GBS disease, provided confidence that our ability to assess maternal antibody status as an independent risk factor for disease was valid.

Risk of Early Onset Disease Predicted by Maternal CPS-Specific Antibody Concentration in Serum at Delivery

The distributions of CPS-specific antibody concentrations in delivery sera of mothers giving birth to neonates who developed early onset Ia, III, or V GBS invasive disease and those whose infants remained well despite exposure to these organisms are summarized in Figure 1 and Table 2. For each GBS CPS type studied, the distribution of maternal IgG serum concentrations for cases was shifted toward lower values, supporting a role for maternal CPS-specific antibody as a protective factor. Relative risks were computed, with the reference group being mothers with CPS-specific IgG concentrations of <0.1 μg/mL (Table 3). For capsular types Ia and III, maternal Ia or III CPS-specific IgG serum concentrations of at least 0.5 μg/mL were associated with a relative risk for neonatal disease of approximately 0.1, corresponding to an approximately 90% reduction in risk ($P = .02$ for each CPS type). For capsular type V, the relative risk, 0.29, was more marginal and corresponded to an approximately 70% reduction in risk. For each of the 3 capsular types, intermediate CPS-specific IgG concentrations (0.1 to <0.5 μg/mL) were associated with a partial reduction in risk

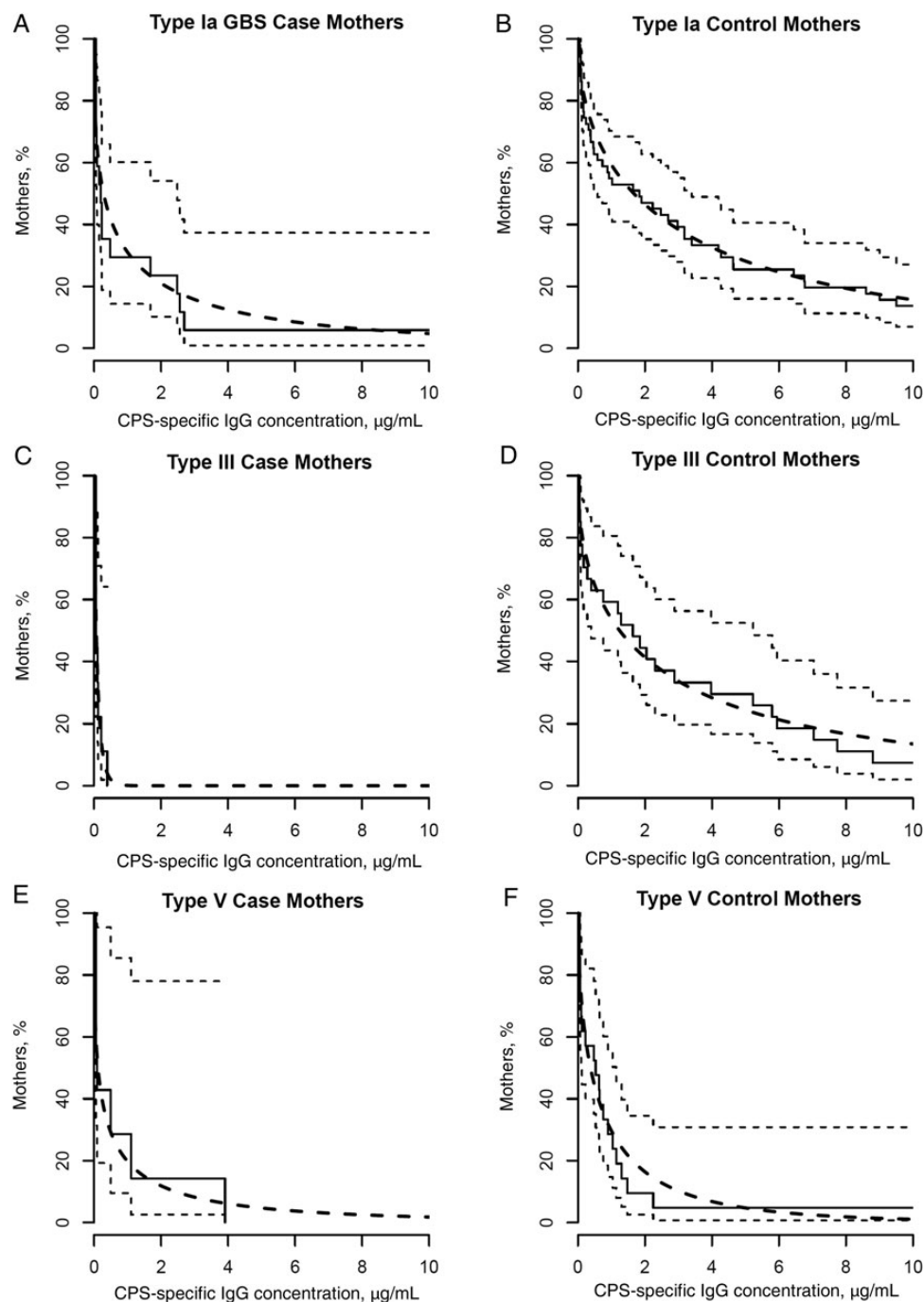**Figure 1.** Shown is the percentage of mothers (cases [*A*, *C*, and *E*] and controls [*B*, *D*, and *F*]) with group B streptococcal (GBS) capsular polysaccharide (CPS)–specific immunoglobulin G (IgG) serum concentrations greater than or equal to the value shown on the horizontal axis. The solid lines display the actual data; the dashed lines indicate the 95% confidence intervals. The width of these confidence intervals depends on both the distribution of the observed values and the number of mothers. The confidence intervals are narrower for Ia controls principally because there were more values for cases and controls. The bolded dashed lines are fitted Weibull functions based on the observed data.

relative to those with concentrations of <0.1 μg/mL. When maternal diabetes mellitus status was taken into account, this did not alter the relationship between CPS-specific antibody concentration in the mother's delivery serum and neonatal disease status. In addition, there was no significant difference between

cases and controls in the proportion of newborn infants who were exposed to maternal intrapartum antibiotics (17% vs 19%; *P* = 1.00).

The predicted absolute risks of early onset disease in infants born to women with GBS CPS–specific serum antibody

Table 2. Maternal Serum Concentrations of Group B Streptococcal Capsular Polysaccharide–Specific Immunoglobulin G (IgG) at Delivery

	IgG Concentration, µg/mL, Median (IQR)		
Population	CPS Type Ia	CPS Type III	CPS Type V
Mothers of case neonates	0.20 (0.06–1.68)	0.060 (0.02–0.12)	0.09 (0.04–0.80)
Colonized mothers of healthy neonates	1.83 (0.20–5.54)	1.64 (0.14–5.51)	0.53 (0.07–1.0)

Abbreviation: IQR, interquartile range.

concentrations at delivery exceeding specified levels are displayed in Figure 2. For each GBS CPS type, the risk of disease in the entire neonatal population born to women colonized with that type with no prevention strategy (eg, no intrapartum antibiotic prophylaxis) was assumed to be 1% [23]. For type III, the predicted risk fell very rapidly as maternal CPS type–specific IgG concentration increased, implying nearly complete elimination of risk for early onset infection when concentrations exceeded 0.45 µg/mL. For type Ia, the predicted risk declined more gradually. While the overall shape of the relationship between disease risk and IgG level for type V was similar to that for type Ia, the estimate was far less certain, as manifested by a higher 75% credibility limit. With the overall attack rate assumption of 1 neonatal case per 100 live births to women with GBS colonization at delivery (1.00), the predicted attack rates at CPS type–specific IgG concentrations of ≥2 µg/mL were 0.49 cases per 100 live births for type Ia, 0 cases per 100 live births for serotype III, and 0.45 cases per 100 live births for serotype V.

DISCUSSION

Our results provide compelling evidence that a sufficient concentration of maternal serum GBS CPS-specific antibody at delivery confers substantial protection to the neonate against early onset disease caused by types Ia and III. These findings are consistent with the demonstrated protection by immune serum in murine models of lethal GBS infection [25] and with observational and case-control studies in humans [3, 4, 6, 26, 27]. Our data also permitted prediction of the absolute risk of early onset GBS disease as a function of a given CPS-specific IgG concentration in a population of pregnant women at delivery. For example, the concentration of type III CPS–specific IgG required to diminish or eliminate the risk of neonatal type III disease was lower than the concentration necessary to effect a similar risk reduction for type Ia. While the risk reduction for type V was not significant, in part because of the smaller number of cases, the trend was similar. This information can be combined with CPS-specific GBS disease rates to estimate the total burden of disease that could be influenced by increasing maternal CPS type-specific IgG concentrations through immunization.

The relative (conditional logistic regression) and absolute (Bayesian framework) risk analyses provide complementary information about the role of maternal GBS CPS–specific IgG in the protection of neonates from early onset GBS infection, but they have limitations. Results of logistic regression analysis decisively affirmed the inverse relationship between maternal antibody concentration at delivery and disease risk in neonates exposed to GBS types Ia or III by their colonized mothers and, possibly, are consistent with a similar effect for type V. One limitation of logistic regression in this context, however, was the need to compare the risk for individuals to that of a reference group, typically those with little or virtually no maternal antibody. This did not allow a straightforward prediction of the risk of disease in a population of pregnant women with specified distributions of CPS-specific antibody concentrations. An additional limitation of logistic regression is the requirement either to specify arbitrary break points in antibody concentrations that corresponded to potentially clinically meaningful differences of risk (eg, >1.0 µg/mL vs <0.1 µg/mL) or to specify the functional form of the antibody-risk relationship (eg, linear or logarithmic).

The Bayesian evaluation of absolute disease risk (Figure 2) avoids these 2 limitations. Our analysis demonstrates that at a type III CPS–specific antibody concentration of ≥0.45 µg/mL in

Table 3. Association Between Early Onset Group B Streptococcal Disease in Neonates and Maternal Serum Capsular Polysaccharide (CPS)–Specific Immunoglobulin G (IgG) Concentrations at Delivery

	CPS Type Ia		CPS Type III		CPS Type V	
CPS-Specific IgG Concentration	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
<0.1 µg/mL (Reference)	. . .		. . .		. . .	
0.1 to <0.5 µg/mL	0.32 (.26–2.52)	.40	0.82 (.01–90.00)	1.00	0.69 (.01–9.06)	1.00
≥0.5 µg/mL	0.11 (.01–.74)	.02	0.09 (.00–.72)	.02	0.29 (.01–3.10)	.50

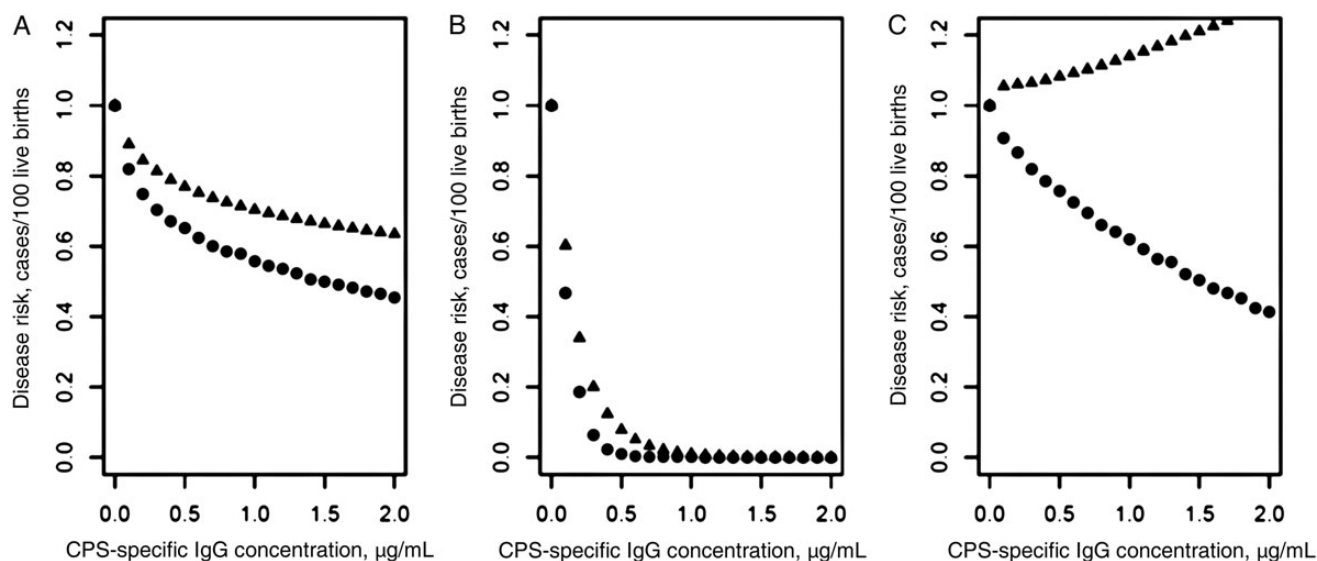Abbreviations: CI, confidence interval; OR, odds ratio.

Figure 2. Bayesian estimate of absolute risk of early onset group B streptococcal (GBS) disease in a neonate born to a colonized mother as a function of capsular polysaccharide (CPS)–specific immunoglobulin G (IgG) concentration in maternal serum at delivery. *A*, Results for capsular type Ia. *B*, Results for capsular type III. *C*, Results for capsular type V. The most likely value, or posterior mode (black circles), and the upper 75th percentile credibility limit (triangles) that a neonate born to a colonized woman with a given CPS-specific IgG concentration will have early onset GBS disease caused by that CPS type are shown. Absolute infection risk estimates were calculated separately for each CPS-specific IgG value.

maternal serum at delivery, the most credible predicted early onset disease risk in the neonate exposed to type III GBS is zero. At maternal antibody concentrations of 1.2 µg/mL, not only is zero the most credible predicted risk, but the posterior odds are 3:1 against any risk. For serotypes Ia and V, the predictions of early onset disease risk never reached zero over the range of concentrations observed in our patients. Instead, for maternal type Ia or V CPS–specific IgG serum concentrations between 1 and 2 µg/mL, the most probable predicted risks were between 0.5 and 0.3 cases per 100 live births, corresponding to 50%–70% reductions relative to the risk in the general population of colonized women.

Several multicenter studies of early onset disease in the United States indicate that GBS types Ia (37%), III (31%), and V (14%) account for >80% of 724 case isolates [15, 26, 27]. Combining these disease frequencies with the predicted influence of raising maternal Ia, III, and V CPS–specific antibody concentrations to ≥1 µg/mL would result in a 70% reduction in the occurrence of neonatal disease caused by these 3 CPS types. Presumably, higher concentrations would further reduce the disease burden. In addition, if late-onset (at 7–89 days of age) GBS disease cases are added to the early onset disease burden, 57% of cases are caused by type III strains [28]. One would expect that the low maternal type III CPS–specific IgG concentrations associated with protection make it plausible that vaccine-induced specific IgG would persist in the young infant through the age at risk for late-onset disease, especially given the reported 10 µg/mL geometric mean concentration of

functionally active antibody in delivery serum of women immunized with a type III glycoconjugate vaccine at 30–32 weeks of gestation [28].

The predicted protective maternal type Ia and III CPS–specific IgG concentrations in our study are substantially lower than those reported by Lin et al for types Ia and III [29, 30]. Those investigators observed in a similar case-control study that the probability of developing early onset disease caused by type Ia and III GBS declined significantly with increasing maternal serum concentrations of GBS type Ia– or III–specific IgG, and they concluded that the risk was reduced by 88% and 91%, respectively, if the maternal concentration was 5 or ≥10 µg/mL. Their higher estimated "protective" levels for type Ia and III CPS–specific IgG most probably are related to differences in serologic methods used for measurement and/or criteria for selection of controls. Importantly, each study provides convincing evidence that a "sufficient" concentration type Ia and III CPS–specific antibody in maternal serum is protective against neonatal early onset type Ia GBS disease. Our study also provided predicted protective maternal concentrations for type V and found that this is substantially lower than concentrations reported in the sera of healthy women who have been immunized with GBS type V glycoconjugate vaccines [12]. Recipients of 2 different type V glycoconjugate vaccines had geometric mean concentrations of 6.5 and 8.9 µg/mL (95% confidence intervals, 2.7–22.4 and 3.5–24.2 µg/mL, respectively) 4 weeks after immunization [12]. The CPS-specific IgG concentrations

elicited following immunization with GBS type Ia and III glycoconjugate vaccines are even higher [9, 11], with levels quite sufficient to confer substantial protection on neonates. Importantly, the concentrations of maternal CPS-specific IgG associated with neonatal protection reported here correlate with opsonophagocytic activity against types Ia, III, and V in human vaccine trials [9, 11, 12] and in sera from infants aged 1 and 2 months born to women immunized with a type III glycoconjugate vaccine at 30–32 weeks' gestation [28].

In summary, our results indicate that relatively low concentrations of GBS CPS–specific IgG in maternal sera at delivery protect most neonates exposed to types Ia, III, and, possibly, V against invasive early onset infection caused by these 3 types. Serum concentrations that correlated with protection against substantial proportions of disease should be readily achieved following immunization with candidate GBS Ia, III, and V polysaccharide-protein conjugate vaccines [9, 11, 12]. The optimal concentrations of CPS-specific IgG required to achieve specific disease reductions will depend on the quantitative relationships demonstrated here and on the prevalence of GBS types associated with early onset GBS disease in specific geographic regions. While maternal immunization with a GBS glycoconjugate vaccine has the potential for protection against not only early onset and late-onset disease, as well as GBS-specific maternal morbidities, such as preterm delivery and chorioamnionitis, it is likely that the need for intrapartum antibiotic prophylaxis will persist for obstetrical patients with gestations of <34 weeks.

Notes

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