Risk Factors for Early-onset Group B Streptococcal Sepsis: Estimation of Odds Ratios by Critical Literature Review

William E. Benitz, MD*; Jeffrey B. Gould, MD‡; and Maurice L. Druzin, MD§

ABSTRACT. *Objective.* **To identify and to establish the prevalence of ORs for factors associated with increased risk for early-onset group B streptococcal (EOGBS) infection in neonates.**

Study Design. **Literature review and reanalysis of published data.**

Results. **Risk factors for EOGBS infection include group B streptococcal (GBS)-positive vaginal culture at delivery (OR: 204), GBS-positive rectovaginal culture at 28 (OR: 9.64) or 36 weeks gestation (OR: 26.7), vaginal Strep B OIA test positive at delivery (OR: 15.4), birth weight ≤ 2500 g (OR: 7.37), gestation <37 weeks (OR: 4.83), gestation <28 weeks (OR: 21.7), prolonged rupture of membranes (PROM) >18 hours (OR: 7.28), intrapartum fever >37.5°C (OR: 4.05), intrapartum fever, PROM, or prematurity (OR: 9.74), intrapartum fever or PROM at term (OR: 11.5), chorioamnionitis (OR: 6.43). Chorioamnionitis is reported in most (88%) cases in which neonatal infection occurred despite intrapartum maternal antibiotic therapy. ORs could not be estimated for maternal GBS bacteriuria during pregnancy, with preterm premature rupture of membranes, or with a sibling or twin with invasive GBS disease, but these findings seem to be associated with a very high risk. Multiple gestation is not an independent risk factor for GBS infection.**

Conclusions. **Mothers with GBS bacteriuria during pregnancy, with another child with GBS disease, or with chorioamnionitis should receive empirical intrapartum antibiotic treatment. Their infants should have complete diagnostic evaluations and receive empirical treatment until infection is excluded by observation and negative cultures because of their particularly high risk for EOGBS infection. Either screening with cultures at 28 weeks gestation or identification of clinical risk factors, ie, PROM, intrapartum fever, or prematurity, may identify parturients whose infants include 65% of those with EOGBS infection. Intrapartum screening using the Strep B OIA rapid test identifies more at-risk infants (75%) than any other method. These risk identifiers may permit judicious selection of patients for prophylactic interventions.** *Pediatrics* **1999;103(6). URL: http://www.pediatrics.org/cgi/content/full/103/6/e77;** ***group B streptococcus, neonatal sepsis, early-onset sepsis, risk factors, prevention.***

From the Departments of *Pediatrics and §Gynecology and Obstetrics, Stanford University, School of Medicine, Stanford, California 94305; and ‡Maternal and Child Health Program, School of Public Health, University of California, Berkeley, California.

Received for publication Oct 1, 1997; accepted Jan 27, 1999.

Reprint requests to (W.E.B.) Division of Neonatal and Developmental Medicine, 750 Welch Rd, Suite 315, Palo Alto, CA 94304. E-mail: benitzwe@leland.stanford.edu

ABBREVIATIONS. GBS, group B streptococcus; EOGBS, early-onset neonatal GBS infection; ACOG, American College of Obstetricians and Gynecologists; AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; LBW, low birth weight (≤2500 g); PROM, prolonged rupture of membranes (>18 hours).

Early-onset group B streptococcal sepsis (EOGBS) has been the leading cause of death attributable to infection in newborn infants for nearly 3 decades,[1] with >6000 cases a year in the United States.[2] The attack rate has not changed over the past 20 years, but the case-fatality rate has declined from ~50% to between 10% and 15%.[3–5] Long-term morbidity among survivors, particularly neurodevelopmental disabilities in those with meningitis, remain distressingly common.[6–9] EOGBS disease may be rapidly progressive and many infants (especially at term) do not exhibit clinical signs of infection initially[5]; therefore, empirical therapy is often initiated because of clinical risk or minimal signs of disease and continued until infection has been excluded by laboratory studies and a period of observation. This aggressive approach has been associated with improved outcomes for infants with this disease,[10,11] but also may lead to acute-care hospitalization and treatment of >100 000 newborn infants yearly in the United States. Social impacts are substantial, ranging from neonatal death to impaired mother–infant bonding and delayed or ineffective establishment of breastfeeding in healthy infants who are separated from their mothers for empirical therapy. Economic costs of empirical treatment of a large number of infants at risk, treatment of infants with confirmed infection, and long-term care for survivors were estimated to exceed $700 million/year in 1985.[12] Therefore, effective methods for prevention have been sought for >2 decades.[13]

In July 1992, the American College of Obstetricians and Gynecologists (ACOG) issued a technical bulletin on group B streptococcal infections in pregnancy,[14] and in November of 1992, the American Academy of Pediatrics (AAP) published its guidelines for prevention of group B streptococcal infection by chemoprophylaxis.[15] Both statements endorsed intrapartum antimicrobial chemoprophylaxis to reduce the incidence of early-onset neonatal disease. The AAP advocated screening for GBS colonization at 28 weeks gestation and giving prophylaxis to GBS-colonized mothers who have clinical risk factors. ACOG contended that antepartum screening cultures are not useful, and advocated prophylaxis for all moth-

ers with clinical risk factors. Several commentaries and clarifications have addressed these differences,[16–20] but both obstetric[19,21] and pediatric[22] practices remained inconsistent. Seeking a consensus, the Centers for Disease Control and Prevention (CDC) convened a multidisciplinary conference in 1995 and issued recommendations for prevention of perinatal GBS disease in May of 1996.[23] ACOG endorsed these recommendations, but expressed concerns about lack of clinical trials or experience with the proposed strategies and potential sequelae of widespread intrapartum antibiotic therapy.[24] The AAP Committees on Infectious Disease and on the Fetus and Newborn also ratified those recommendations.[25] However, the recommendations include two strategies for identifying candidates for intrapartum prophylaxis, and yet another strategy has been proposed by Gotoff and Boyer,[26] indicating that efforts to achieve consensus have not been entirely successful.[27] Consensus regarding management of infants, particularly those whose mothers have received intrapartum prophylaxis, has been even more elusive. The sample algorithm for management of such infants[23] that was provided by the CDC and modified slightly by the AAP[25] is only weakly endorsed, ending with admonitions that "other management approaches, developed by individual physicians or institutions, may be appropriate alternatives"[23] and it is "suggested but not an exclusive approach to management."[25]

Uncertainty about and inconsistent perceptions of clinical factors that may identify women who are at risk of having an infant with EOGBS disease are major barriers to achievement of the desired consensus. The medical literature regarding these subjects, which is extensive and highly technical in many respects, has been reviewed extensively,[1,28–31] discussed,[20,23,32–34] and debated.[18,35–37] Despite metaanalyses,[38] critical reviews,[39] cost-benefit studies,[36,40–43] and decision modeling,[44] misapprehensions of risk endure, significant observations are often overlooked, and the essential requirements for high efficacy of interventions intended to reduce the prevalence of neonatal GBS disease have not been articulated clearly. Because of the low prevalence of this disease, the number of enrollees that would be required for randomized trials to evaluate potential treatment or prevention regimens has been described as prohibitive.[20] For the present, at least, rational approaches to prevention of GBS disease in neonates will have to be based on existing knowledge.

Accurate ascertainment of risk to enable selection of a target population for intervention is a crucial first step in development of prevention programs. Effective programs for prevention of neonatal GBS disease should address populations that include the fewest possible mothers along with the greatest number of infants who will have GBS infections. Intervention strategies that address a very small but extremely high-risk segment of the population may have little impact on the overall incidence of disease. If both the prevalence of a risk factor and the associated OR for GBS disease are known, the percentage of infants with GBS disease born to mothers identified by that risk factor can be calculated. Then, the distribution of GBS cases can be used to assess the efficiency with which GBS prevention strategies identify infants at risk. Evaluation and comparison of risk ascertainment strategies depends on knowledge of the identity, prevalence, and ORs for clinical findings associated with EOGBS, which must be both reliable and internally consistent. We have reviewed critically and reevaluated published data with meticulous attention to technical details and mathematical rigor to identify and establish the prevalence and ORs for risk factors of EOGBS disease.

METHODS

Clinical conditions associated with EOGBS were identified through a search of MEDLINE, as well as reference lists for those articles and recent reviews of neonatal GBS disease.[1,17,30,34,45] Prevalence rates for prematurity and low birth weight (LBW) were abstracted from the 1991 national[46] or 1992 California birth cohorts. All available data were evaluated to establish the prevalence of each identified risk factor. Because the attack rate observed in association with a risk factor is dependent on the overall attack rate in the population included in that particular study, as well as the associated OR for GBS sepsis, raw attack rates should not be extrapolated from such samples to other populations. Although relative risk is easy to understand and apply to clinical practice, this risk parameter is not suitable for application to other populations or distribution of risk among subgroups within populations. Therefore, the OR, which is the most robust parameter for such extrapolations,[47] is used throughout this analysis. All risk predictions are based on the same demographics (GBS colonization and attack rates, prevalence of prematurity, etc); therefore, risk estimates for different subgroups could be compared directly. Whenever possible, multiple sources were consulted to ensure external validity for each prevalence and OR estimate. Infants were considered to have GBS infection only if GBS were recovered from nonpermissive cultures, ie, blood or cerebrospinal fluid. Infants with clinical findings consistent with sepsis or with positive tests for urinary GBS antigen, who did not have positive nonpermissive cultures, were not considered to have GBS infection. CIs for ORs were calculated using the method of Cornfield,[48] and CIs for prevalence rates were calculated using the binomial[49] or normal[50] distributions, as appropriate. Ratios were compared using the G test of independence, a preferred alternative to the χ^2 or Fisher exact tests for contingency tables in which the marginal totals are not fixed by experimental design.[51] Gradients of risk in groups ordered by density of GBS colonization, gestational age, or birth weight were evaluated using the method of Bartholomew.[52] Formulas for probabilities of GBS disease in the presence or absence of a risk factor were derived from the definition of OR.[53] For factors with >2 possible values, eg, gestational age, the probability of falling into the lowest-risk category for that factor and having GBS disease ($x = P_{F1+D}$) was calculated from the equation:

$$\sum_{i=1}^{n} \frac{OR_i P_{Fi} x}{(P_{F1} - x) + OR_i x} = P_D$$

solving for x numerically using an iterative method. (P_{Fi} is the population fraction with risk factor i, OR_i is the corresponding OR, P_D is the prevalence of disease, and the subscript 1 denotes the lowest risk category.) For dichotomous factors, eg, presence or absence of intrapartum fever, the probability that an infant has both the risk factor and GBS disease ($x = P_{F+D}$) was calculated by solving the equation:

$$(1 - OR)x^2 + [OR \cdot P_F + (1 - P_F) + (OR - 1)P_D]x - OR \cdot P_D \cdot P_F = 0$$

for x using the quadratic formula. (P_F is the prevalence of the risk factor, OR is the corresponding OR, P_D is the prevalence of disease.) Other elements of each contingency table were derived from these values. Sensitivity, specificity, and positive and predictive negative values were calculated using standard formulas.[54]

RESULTS

Population Attack Rates for EOGBS

Reported population attack rates for EOGBS disease in the United States range from .76 to 5.46 cases per 1000 live births (Table 1). Data gathered since 1985 suggest a typical attack rate of ~1.8 cases per 1000 deliveries (.0018). In a population with an intrapartum vaginal colonization rate of 14.7%,[55] the risk among infants born to GBS carriers would be ~12.2/1000 live births (.0122), which is at the lower end of empirically determined attack rates among such infants (.011–.092).[56–63] Because this attack rate is based on culture-proven GBS disease, and because single small-volume blood cultures routinely used in neonates do not yield an organism in many infants with invasive bacterial disease,[64,65] this undoubtedly underestimates the true incidence of GBS disease. For decision analysis, the attack is estimated to be 3 cases per 1000 live births (1.8 culture-proven cases per 1000 live births divided by a culture sensitivity of 60%).[65]

Maternal GBS Colonization

Because the association between the presence of the organism in the birth canal and invasive neonatal disease was recognized soon after the emergence of GBS as a major cause of neonatal infections in the late 1960s, the epidemiology of maternal colonization has been investigated extensively. These studies have defined clearly the requirements for optimal ascertainment of maternal colonization. To maintain viability of the organism en route to the laboratory, swabs or washes should be placed immediately into transport medium, eg, Amies' or Stuart's medium.[66] Specimens should be inoculated into selective broth medium, eg, Todd-Hewitt medium supplemented with colistin and nalidixic acid, and subcultured 18 to 24 hours later on blood agar plates.[58,67–70] Direct plating of specimens onto blood agar plates may underestimate colonization rates by up to 50%.[67,68,71–76] Swabs or washes of the lower third of the vagina are more likely to reveal colonization than those obtained from the vaginal fornices or endocervix.[77] Rectovaginal colonization rates exceed vaginal colonization rates by ≥50%[57,78,79] (Table 2). Both vaginal and rectal colonization may be persistent, transient, or intermittent,[57,79–82] limiting the predictive value of screening cultures for colonization on any future date.

Reported colonization rates in pregnant women range from 2% to 35%.[1,45] This variation has been attributed to use of different culture methods, particularly culture of different anatomic sites and use of selective broth versus direct inoculation of agar plates. Geographic differences, with low colonization rates reported from countries in which neonatal GBS infection is uncommon, also contribute. Even with consistent technique, cross-sectional studies from the United States in which vaginal or rectovaginal specimens from pregnant women were cultured in selective broth medium show substantial variation in colonization rates (Table 2). Ethnicity, maternal age and parity, marital status, education, smoking, and frequent intercourse with multiple partners[80,83] also may influence the prevalence of colonization, but relationships among these factors and GBS colonization may be inconsistent. For example, Hispanic patients had the highest colonization rates in New York but the lowest rates in Washington, Oklahoma, and Louisiana, compared with other ethnic groups.[83] These risk factors may raise clinical suspicion for GBS colonization but do not identify high-risk women for whom selective screening might be appropriate.[83]

Maternal vaginal colonization with GBS is essen-

TABLE 1. Attack Rates for EOGBS (US)

Location	Dates of Survey	EOGBS Cases/ Total Newborns	Attack Rate (/1000 Births)	References
Colorado	Aug 1969–Dec 1971	6/1940	3.09	149
New York, NY	Nov 1970–Feb 1974	12/15 726	0.76	101
Dallas, TX	Jan 1972–Dec 1977	69/43 333	1.59	150
Chicago, IL	Jan 1972–Dec 1979	101/54 228	1.86	151
Houston, TX	Aug 1972–Nov 1972	15/4385	3.42	152
Palm Beach, FL	Sept 1972–Dec 1972	1/242	4.13	153
Houston, TX	1973–1982	185/117 981	1.57	106
Chicago, IL	Jan 1973–Dec 1981	61/32 384	1.88	55
Minneapolis, MN	Jan 1975–Dec 1983	13/7960	1.63	154
Washington, DC	Jan 1975–Dec 1984	19/≈8300	2.3	155
Birmingham, AL	July 1977–July 1978	13/5511	2.36	142
Dallas, TX	Dec 1977–May 1981	19/15 976	1.19	156
Birmingham, AL	Jan 1978–Dec 1983	24/13 753	1.75	86
Rochester, NY	Jan 1979–Dec 1989	92/20 662	4.45	4
Atlanta, GA	Jan 1982–Dec 1983	71/64 858	1.09	3
Dallas, TX	Nov 1986–Dec 1994	234/119 931	1.95	150
Four cities*	Jan 1987–Dec 1989	197/61 809	3.19	5
Hartford, CT	1989–1994	26/26 525	1.00	139
Four regions†	Jan 1990–Dec 1990	247/≈180 000	1.4	2
Five regions‡	Jan 1991–Dec 1991	410/≈230 000	1.8	111
Jackson, MS	May 1991–Oct 1992	32/5865	5.46	157
Northern IL	Jan 1993–June 1994	21/10 021	2.10	109

* Atlanta, Denver, Kansas City, Washington DC.
† San Francisco Bay area, four Tennessee counties, metropolitan Atlanta, state of Oklahoma.
‡ San Francisco Bay area, four Tennessee counties, metropolitan Atlanta, Maryland, and Missouri.

TABLE 2. Prevalence of Maternal Colonization With GBS During Pregnancy

Vaginal Colonization				
Author, Year	GBS+	Total	Rate (%)	Reference
Lewin, 1981	50	722	6.9	158
Bobitt, 1985	51	718	7.1	159
Iams, 1982	97	1304	7.4	160
Allardice, 1982	164	2169	7.6	59
Badri, 1977*	81	769	10.5	78
Dillon, 1982*	98	754	13.0	79
Kontnick, 1990	64	434	14.8	74
Boyer, 1983*	820	5586	14.7	57
Anthony, 1978	57	382	14.9	80
Yancey, 1993	63	365	17.3	161
Park, 1996	100	531	18.8	92
Pass, 1979	216	1142	18.9	56
Carroll, 1996	184	962	19.1	76
Dillon, 1987	1523	7627	20.0	86
Anthony, 1981	13	64	20.3	93
Regan, 1996	2877	13 646	21.1	87
Baker, 1973	46	205	22.4	152
Armer, 1993	44	192	22.9	90
Morales, 1986	297	1207	24.6	60
Jones, 1983	54	201	26.9	162
Beachler, 1979	32	112	28.6	163
Clark, 1992	92	314	29.3	76
Rectovaginal Colonization				
Author, Year	GBS+	Total	Rate (%)	Reference
Gibbs, 1994	687	3721	18.5	164
Badri, 1977*	142	769	18.5	78
Embil, 1978	90	462	19.5	165
Boyer, 1983*	1272	5586	22.8	57
Boyer, 1986	3087	13 381	23.1	62
Dillon, 1982*	211	754	28.0	79

* Direct comparisons of vaginal and rectovaginal colonization rates.

tially a prerequisite for both early colonization of the newborn infant and EOGBS.[56,59,84–87] Data demonstrating the relationship between intrapartum colonization of the vagina and EOGBS sepsis (Table 3) are quite compelling (OR: 204; 95% CI: 100–419). Data that address the relationship between the density of maternal colonization and neonatal GBS sepsis have become available only recently.[87,88] Compared with infants whose mothers are lightly colonized, infants whose mothers have heavy genitourinary GBS colonization are more likely to become colonized,[57,60,85,89] and the risk for GBS infection is much greater in heavily colonized neonates.[56] Yancey et al[88] stratified maternal colonization within the last 2 weeks before delivery from 0 to 4+ according to the number of quadrants in which GBS colonies were observed on blood agar plates inoculated directly with vaginal swabs and streaked in a standardized sequence; a ranking of 0 was assigned for those women for whom GBS was isolated only in enriched broth.[90] Regan et al[87] defined heavy colonization at the time of delivery as isolation of GBS by direct culture on nonselective solid media and light colonization as isolation of GBS only by subculture of selective broth media; this definition has been adopted for this discussion. As shown in Table 4, these studies show gradients in risk with increasing colonization density ($P < .005$ by Bartholomew's test[52]). With heavy colonization in 71.8% of women with GBS-positive vaginal cultures[76,91,92] and odds of infection that is 2.54 times greater in infants of heavily colonized, compared with lightly colonized, mothers,[87] the ORs for EOGBS in infants of lightly and heavily colonized women are 97.1 and 247, respectively.

Results of cultures are not available for 36 to 48 hours, thus cultures obtained on presentation for delivery cannot guide intrapartum interventions or early initiation of neonatal treatment. Prediction of colonization status at delivery by performing cultures during pregnancy is imperfect, because women may lose or acquire GBS colonization between screening and delivery,[57,59,84,93] producing false-positive or false-negative results. In 12 935 women screened for vaginal and endocervical colonization at 23 to 26 weeks, the OR for infection associated with positive cultures was only 1.65 (95% CI: .70–3.91), and only 30% of neonates with EOGBS disease were born to mothers with positive cultures.[87] Yancey et al[88] recently reported an OR for neonatal sepsis of only 4.36 (95% CI: 1.59–11. 9) in association with GBS-positive cultures of vaginal swabs obtained within 2 weeks before delivery,[88] confirming that even vaginal cultures obtained late in gestation are much less effective than cultures obtained at delivery. Because the rectum may provide a reservoir from which the genitourinary tract may be intermittently recolonized,[79,94] addition of rectal specimens or anorectal specimens to vaginal specimens has been recommended. This identifies up to twice as many colonized women,[78,79] and increases the predictive value of antenatal cultures for vaginal colonization at delivery.[72] Boyer et al[55] found that positive rectovaginal screening cultures performed late in the first to

TABLE 3. Association of Early-onset Neonatal GBS Sepsis With Maternal Vaginal Colonization at Delivery

Author, Year	Maternal Vaginal Culture at Delivery				References
	GBS+		GBS−		
	EOGBS Cases	Total Subjects	EOGBS Cases	Total Subjects	
Pass, 1979	7	216	0	926	56
Allardice, 1982	9	136	0	1970	59
Dillon, 1987	24	1523	0	5104	86
Regan, 1996	9	568	1	2301	87
Total	49	2443	1	10 301	

Sensitivity = 98.00%, specificity = 81.14%, positive predictive value = 2.01%, negative predictive value = 99.99%, Mantel-Haentszel OR = 204 (95% CI: 100–419); $P < .001$.

TABLE 4. Density of Maternal Vaginal Colonization and Risk of Early-onset Neonatal GBS Sepsis

GBS Colonization*	EOGBS Cases	Total Subjects	OR (95% CI)	*P*†		References
				All Groups	GBS+ Groups	
No GBS	6	607	1.0	<.005†	<.005†	88
1+ GBS	1	95	1.07 (0.17–6.85)			
2+ GBS	3	68	4.62 (1.24–17.3)			
3+ GBS	5	53	10.4 (3.26–33.5)			
Any GBS	9	216	4.36 (1.59–11.9)	.007‡	(Versus No GBS)	
No GBS	1	2301	1.0	<.005†	.227‡	87
Light GBS	2	237	19.6 (2.55–150)			
Heavy GBS	7	331	49.7 (7.94–310)			
Any GBS	9	568	37.0 (6.05–226)	<.001‡	(Versus No GBS)	

* Density of colonization categorized as described in text, after Yancey et al[88] and Armer et al.[90] Yancey et al[88] screened for colonization within the last 2 weeks before delivery, Regan et al[87] screened at delivery.
† Test for gradient in attack rates with increasing levels of colonization, including or excluding infants whose mothers have negative vaginal cultures, respectively, by Bartholomew's χ^2 method. Significant tests for presence of a gradient correlate with contingency table analysis by *G* test of independence (results not shown).
‡ Comparison of GBS-colonized to noncolonized subjects by *G* test of independence.

early in the third trimester were associated with an OR of 29.4 (95% CI: 7.44–116) for EOGBS sepsis, which compares quite favorably with the OR associated with vaginal colonization identified at 23 to 26 weeks (1.65)[83] or during the last 2 weeks of gestation (4.36).[88] The AAP and CDC recommendations emphasize correctly that antepartum screening cultures must be performed using swabs from both the vaginal introitus and anorectum.[15,23]

The predictive values of screening cultures performed at different stages of pregnancy are critical to selection of the optimal time for antepartum screening. The predicted colonization rate at delivery, *C*, is determined by the equation $C = S \times P + (1 - S) \times (1 - N)$, where *S* is the prevalence of a positive screening culture and *P* and *N* are its positive and negative predictive values for colonization at delivery, respectively. These predictive values and the prevalence of vaginal colonization are determined by the rates at which GBS rectovaginal colonization is lost or acquired by colonized and noncolonized women, respectively, and by the proportion of women with rectovaginal colonization who have vaginal colonization. Arbitrary selection of positive and negative predictive values of antepartum cultures implicitly selects values for rates of loss and acquisition that are almost certain to be different and inconsistent with the colonization rate, which is determined by these conversion rates (colonization rate = acquisition rate ÷ sum of acquisition and loss rates). The resulting artifactual shifts in the vaginal colonization rate expected at delivery distorts the predicted GBS attack rate. Only one previously published model recognizes this significant source of bias in decision analysis models[43] that is a serious flaw in the model on which the recent CDC recommendations are based.[44] For this analysis, predictive values for antepartum cultures were derived from the most comprehensive single dataset available.[55] The rates of loss and acquisition of rectovaginal colonization were determined to be 2.46% and .72%/week, respectively,[57] by linear regression of the log of conversion fraction against time between cultures. The prevalence of vaginal colonization among women with rectovaginal colonization in that study was 64.5%. These rates of loss and acquisition of colonization were used to calculate internally consistent predictive values for antepartum rectovaginal cultures. Cultures at 28 weeks have positive and negative predictive values for vaginal colonization at delivery of 48.7% and 95.3%, respectively; at 36 weeks the predictive values are 58.2 and 98.2% (Table 5). These estimates are near the middle of the ranges of reported values (corrected for different vaginal and rectovaginal colonization rates, as appropriate),[57,59,82,84] and closely approximate recently reported empirical values (56.1% and 97.4% for vaginal colonization).[95]

The association between vaginal colonization at delivery and EOGBS infection has been a powerful impetus for development of prevention strategies based on ascertainment of maternal GBS colonization. This approach is central to the strategies advocated by the AAP[15] and the CDC,[23] but there are

TABLE 5. Characteristics of Screening Tests for Intrapartum Maternal Vaginal Colonization*

Screening Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Rectovaginal culture at 28 wks	75.5	86.3	48.7	95.3
Rectovaginal culture at 36 wks	90.8	88.9	58.6	98.2
Strep B OIA	70.8	92.7	62.7	94.9

* Values calculated for a population with vaginal and rectovaginal colonization rates of 14.7% and 22.8%, respectively. Data for Strep B OIA based on a population in which 72% of colonized patients had heavy colonization.[76,91,92]

barriers to implementation. Practical as well as epidemiologic considerations will influence selection of methods for identification of women who have or are likely to have vaginal GBS colonization at delivery. Among the greatest barriers to general acceptance of antenatal screening strategies is inability to ensure that screening cultures are performed consistently and that results are available at the site and time of delivery.[23,96] A policy of antepartum screening may expose obstetricians to an untenable medicolegal risk, particularly in cases of EOGBS infection in an infant whose mother was not screened on schedule or for whom the screening culture result was not available in the labor and delivery suite, leading to omission of intrapartum prophylaxis.[97,98] Antepartum screening cultures require collection of rectal, as well as vaginal, samples, which many obstetricians believe to be unacceptable to their patients.[99] Therefore, a diagnostic method that permits rapid, easy, and accurate identification of GBS-colonized parturients on presentation for delivery would be ideal for ensuring immediate and consistent ascertainment of GBS colonization. Rectovaginal sampling is not necessary at delivery, because virtually all infants with EOGBS disease are born to mothers from whom GBS can be recovered from vaginal cultures. In fact, ascertainment of a larger pool of mothers with rectovaginal colonization would not identify additional infants who are likely to become infected but would enlarge and dilute the pool of women identified as being at risk for that neonatal outcome. Of the currently available methods, only the BioStar Strep B OIA test (Table 6) has performance characteristics sufficient for clinical utility in this application (Tables 5 and 6). Another recent comparison of rapid immunoassays is not included in this summary because a nonstandard sampling method was used.[100] In a population in which 14.7% of women have vaginal colonization (heavy in 71.8%), 52.6%, 10.0%, and 37.3% of parturients with positive intrapartum Strep B OIA tests would be expected to have heavy, light, or no GBS colonization, respectively, and 2.2%, 3.0%, and 94.9% of those with a negative test result are expected to have heavy, light, or no colonization, respectively. Because this test must be performed by skilled laboratory personnel rather than at the bedside, it may be necessary to train a number of laboratory personnel so that the test will be available 24 hours/day. As with any test, such an increase in the number of personnel who perform it may be associated with performance inferior to that described in research protocols.

Prematurity and LBW

The excess risk of EOGBS disease in preterm and LBW infants has been well-recognized for many years. Early reports noted that preterm[101,102] and LBW[101–103] infants were overrepresented among infants with early-onset disease, a finding confirmed by more recent case–control studies.[4,35] Increased risk for infants with birth weights ≤2500 g has been recognized,[86,104] and a gradient of increasing risk with decreasing birth weights <2500 g has also been delineated.[3,5,55,105,106] Yancey et al[88] have recently demonstrated a progressive increase in risk for neonatal sepsis in general with decreasing gestational age. ORs associated with birth weight and gestational age are summarized in Table 7. This analysis confirms a statistically significant gradient of risk with either decreasing gestational age or birth weight. These variables are correlated, but risk is low for infants with birth weights >2500 g and for infants born after 37 weeks gestation. In a multivariate analysis, only the combination of LBW and prematurity was correlated with neonatal pneumonia and sepsis,[107] thus preterm infants of birth weight >2500 g and term infants (including those with birth weights ≤2500 g) may be at a comparably low risk.

The prevalence of prematurity or LBW varies regionally[46] and locally[106] and is an important determinant of the population risk for GBS disease.[106] Because our objective was to evaluate the impact of potential interventions on an entire population, demographic distributions were determined using data from the most recent national (1991) and California (1992) birth cohorts.[46] In these cohorts, the prevalence of prematurity (<37 weeks) was 10.3%, which is the same as the prevalence of prematurity

TABLE 6. Clinical Performance of Strep B OIA Optical Immunoassay for Maternal GBS Colonization*

Subjects	Colonization Rate (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	References
531	18.8	72.0	95.6	79.1	93.6	92
962	20.2	62.4	92.2	66.9	90.7	76
751	13.7	85.4	91.5	61.5	97.5	91

Pooled data from above studies, stratified according to colonization density†

Subjects	Colonization Density‡	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	References
2244	Heavy	82.8	92.7	52.6	94.9	76, 91, 92
	Light	40.2		10.0		

* As compared to cultures in Lim broth.

† Data represent empirically determined specificity and sensitivities for heavy and light colonization applied to a population in which 14.7% of women have vaginal colonization, of whom 72% have heavy colonization.[76,91,92]

‡ Heavy and light colonization are defined as isolation of GBS from nonselective solid media or only in selective broth, respectively. These terms are used differently in reports of clinical evaluations[76,92] and in the manufacturer's description of the test but correspond to those used to stratify risk of neonatal GBS disease.[87]

TABLE 7. ORs for EOGBS Stratified by Birth Weight and Gestational Age

Birth Weight (g)	EOGBS Cases	Live Births	OR (95% CI)	*P*		References
				All Groups	Groups ≤2500 g	
500–1000	10	382	24.8 (12.2–50.2)	<.005*	<.005*	55
1001–1500	4	499	7.45 (2.73–20.3)			
1501–2000	7	798	8.16 (3.66–18.2)			
2001–2500	9	2102	3.96 (1.91–8.20)			
>2500	31	28 603	1.00			
All ≤2500	30	3781	7.37 (4.48–12.1)	<.001†	(vs >2500 g)	
Gestational Age (wks)	EOGBS Cases	Live Births	OR (95% CI)	*P*		References
				All Groups	Groups <37 wk	
<28	1	4	32.1 (4.19–265)	<.005*	<.005*	88
28–30	2	15	14.8 (3.23–70.3)			
31–33	2	30	6.89 (1.56–30.8)			
34–36	3	92	3.25 (.90–11.8)			
≥37	7	682	1.00			
All <37	8	141	5.80 (2.15–15.7)	.0023†	(vs ≥37 wk)	

* Test for gradient in ORs with decreasing birth weight or gestational age, including or excluding infants in the low risk category (>2500 g or ≥37 weeks), respectively, by Bartholomew's χ^2 method. Significant tests for presence of a gradient correlate with contingency table analysis by *G* test of independence (results not shown).
† Comparison of normal with all LBW and term with all preterm subjects, respectively, by *G* test of independence.

reported in a multistate surveillance study of neonatal GBS disease.[2] Only .8% of all deliveries occurred before 28 weeks gestation. The rates of prematurity were 62.5% among infants with birth weights ≤2500 g and 6.86% among larger infants. Birth weight was ≤2500 g in 37.5% of preterm infants. Allocating the increased risk for preterm infants, as described by Boyer et al,[55] to those infants who weigh ≤2500 g permits calculation of an OR of 11.4 for preterm infants ≤2500 g in their population. Applying this relative risk to a population reflecting California and national demographics yields an overall relative risk for all preterm infants of 4.83. Distribution of the risk of GBS infection among the preterm infants according to the ORs defined for each gestational age interval by the data of Yancey et al[88] allows estimation of the ORs and attack rates shown in Table 10.

Onset of labor before term is correlated strongly with subclinical maternal infection,[108] which may contribute to the high prevalence of EOGBS disease in premature infants. The separate contributions of preterm labor and preterm delivery, which are obviously strongly covariant, have not been determined, but spontaneous onset of labor before term should be considered to be a clinical indicator of possible intrauterine infection.

Prolonged or Premature Rupture of the Amniotic Membranes

Prolonged rupture of the amniotic membranes for >18[55,88] to 20[105] hours before delivery substantially increases the risk of neonatal GBS disease[55,88,105,107] (Table 8). Because rupture of membranes for >18 hours was observed in <10% (2 of 21) of mothers whose infants developed GBS sepsis, a recent case–control study has suggested that prolonged rupture of membranes (PROM) >10 hours would be more sensitive.[109] The significance of this observation remains uncertain, because criteria for sepsis were not limited to recovery of GBS from nonpermissive cultures, only term infants were included, and the sample size was small. The largest published series indicates that PROM >18 hours occurs in 12.5% of deliveries and is associated with an OR of 7.28 (95% CI: 4.42–12.0).[55] Premature rupture of the amniotic membranes before the onset of labor occurs in 20% to 25% of pregnancies.[110,111] Premature rupture of membranes is more common among mothers who are GBS-colonized[110] or whose infants have GBS infection,[111] particularly among preterm infants,[5,112] but neither the attack rate nor the OR for these infants can be calculated from available data. Preterm premature rupture of membranes occurs in 1% to 2% of pregnancies[113] and is a significant univariate risk factor for neonatal pneumonia or sepsis (OR: 5.2; 95% CI: 2.4–11.6), even after controlling for prematurity and LBW.[107] Neonates born to GBS-colonized mothers after preterm premature rupture of membranes apparently are at extremely high risk with attack rates of 33% to 50%.[114,115]

Intrapartum Fever

Intrapartum temperature >37.5°C,[55] >38.0°C,[112] or fever without additional definition[45] are associated with an increased risk of neonatal GBS infection. Two studies describe a greater likelihood of intrapartum fever in mothers of infants with confirmed GBS infection,[111,112] but only one study[55] provides data sufficient to calculate an OR for an intrapartum temperature >37.5°C (OR: 4.05; 95% CI: 2.17–7.56). Although pediatricians generally believe that higher maternal fever confers a higher risk, there are no objective data to quantitate that relationship. Cimolai and Roscoe reported GBS bacteremia in 8 of 13 infants born to mothers with a temperature >37.5°C but <38.0°C and in 13 of 30 of infants born to mothers with fevers ≥38.0°C.[116] These attack rates are remarkably high and not significantly different. The prevalence of fever (1/1000 deliveries) in that popu-

TABLE 8. ORs for EOGBS Stratified by Duration of Rupture of the Amniotic Membranes

Duration of ROM (h)	EOGBS Cases	Live Births	OR (95% CI)	*P**		References
				All Groups	Groups ≤18 h	
0–6	4	439	1.0	.024	.76	88
6–12	2	165	1.33 (.28–6.30)			
12–18	2	108	2.05 (.43–9.73)			
>18	7	111	7.32 (2.24–23.8)			
0–6	15	19 665	1.0	<.001	.089	55
7–12	10	5391	2.43 (1.12–5.32)			
13–18	5	3277	2.00 (.76–5.30)			
19–24	11	1943	7.48 (3.48–16.0)			
25–48	11	1276	11.4 (5.32–24.4)			
>48	9	832	14.3 (6.39–32.1)			
0–9	6	9289	1.0	<.001	.71	105
10–19	1	968	1.60 (.25–10.1)			
20–29	6	357	26.5 (8.95–78.2)			
30+	7	383	28.8 (10.1–82.1)			
Pooled data for patients with ROM ≤ or > 18 h or < or ≥ 20 h from above studies.						
≤18	8	712	1.0	.0025		88
>18	7	111	5.92 (2.19–16.1)			
≤18	30	28 333	1.0	<.001		55
>18	31	4051	7.23 (4.42–12.0)			
<20	7	10 257	1.0	<.001		105
≥20	13	727	26.2 (10.7–63.9)			

* Comparison of attack rates for all strata, including or excluding infants in the low risk category (shortest duration of rupture of membranes) by *G* test of independence.

lation was much lower than that reported by others (36–92/1000 deliveries),[55,111,117] thus this study does not refute the hypothesis that higher fevers are associated with greater risk. Obstetricians may diagnose chorioamnionitis, which is associated strongly with fetal and neonatal infection, in any women with a high fever during labor.[118] Women who receive epidural analgesia are more likely to have a fever,[119–124] and their infants are more likely to be evaluated for sepsis and to receive antibiotic therapy.[124] During epidural analgesia, the maternal temperature increases at .08[120,122,123] to .14°C/hour,[119] exceeding 38.0°C in 10% to 15% of women.[121,122,124] However, fevers exceeding 38.5°C seem to be quite rare. Use of a higher fever threshold for women who have had epidural analgesia may be appropriate.[124] Interventions may be appropriate for infants born to mothers who have fevers during labor, but available data do not identify specific temperature thresholds above which prophylaxis, diagnostic screening, or empiric therapy are appropriate or imperative.

Chorioamnionitis

Intrapartum fever accompanied by two or more additional signs, including fetal tachycardia, uterine tenderness, foul-smelling vaginal discharge, or maternal leukocytosis, occurs in 1.0% to 3.8% of parturients and is associated with neonatal GBS attack rates ranging from 6% to 20%.[88,118,125–128] The risk is presumably even greater in GBS-colonized women with chorioamnionitis. The only study that provided sufficient data for estimation of an OR found that chorioamnionitis, as defined above, occurs in 10.0% (95% CI: 9.0–11.0)[88] of pregnancies and is associated with an OR for all early-onset neonatal sepsis of 6.42 (95% CI: 2.32–17.8). This may overstate the prevalence and underestimate the associated risk. Chorioamnionitis was almost universally present in mothers of infants who became septic despite intrapartum prophylaxis with an appropriate intravenous antibiotic (44 of 50 reported cases[5,88,129,130]). Mecredy et al[118] reported bacteremia in 1 of 63 asymptomatic infants and 3 of 23 symptomatic infants whose mothers have received intrapartum treatment for chorioamnionitis. These observations suggest that chorioamnionitis is a marker of high risk for invasive GBS disease, even in infants whose mothers receive antibiotic prophylaxis.

Combined Intrapartum Factors

Seeking a collection of factors associated with a preponderance of EOGBS cases, Boyer et al[55] found that the presence of intrapartum maternal fever (>37.5°C), PROM (>18 hours), and/or birth weight ≤2500 g identified a group including <20% of all infants but nearly 75% of those who develop GBS sepsis. Multistate risk assessments identified intrapartum fever, PROM, and/or prematurity in 75% of mothers of GBS cases in 1991 and 1992,[111] but in only 54% in 1995. Based on the data of Boyer et al,[55] the probability of having one or more of these high-risk factors is 18.3%[55] and the associated OR is 12.6 (95% CI: 7.17–22.2). Both Boyer et al[55] and Rouse et al[44] observed PROM or maternal intrapartum fever in 7.5% of term infants. Excluding infants ≤2500 g, the OR for infants >2500 g whose mothers had fever or

PROM is 11.5 (95% CI: 5.78–23.1). Applying this risk estimate to a population reflecting national prevalences for prematurity and LBW, prematurity, PROM, or intrapartum fever is expected in 17.1% of women and is associated with an OR of 9.74; the prevalence of birth weight ≤2500 g, PROM, or intrapartum fever is 13.3% and the associated OR is 12.3.

Maternal GBS Bacteriuria

Infants born to women with GBS bacteriuria during pregnancy are more frequently and more heavily colonized with GBS[131] and may be at increased risk for invasive GBS disease.[56,132] In 1500 consecutive deliveries, Liston et al[133] reported a high prevalence of pneumonia (39%), suspected sepsis (44%), and GBS bacteremia (6%) among 55 infants whose mothers had GBS in urine cultures routinely obtained after delivery. Although this suggested an association between maternal GBS bacteriuria and neonatal sepsis, this attack rate was not significantly different from that in controls (0 of 41; $P = .09$). Wood and Dillon prospectively identified a 2.5% prevalence of significant ($\geq 10^5$ organisms/mL) GBS bacteriuria during pregnancy.[134] Among 14 pregnancies with this finding, 2 ended in intrauterine fetal demise and 2 were followed by neonatal GBS infections (1 EOGBS scalp abscess and 1 late-onset sepsis). In the only prospective study that provides data permitting direct comparison of attack rates in infants born to mothers with and without GBS bacteriuria, Møller et al[135] also found a 2.5% prevalence of GBS bacteriuria among women prospectively screened between 12 and 38 weeks. They reported 5 cases of confirmed GBS sepsis among 68 infants born to women with compared with 0 cases among 2677 without GBS bacteriuria ($P < .001$). Persson et al[136] prospectively screened women for asymptomatic bacteriuria on three occasions during pregnancy and identified 1 infant with GBS disease among those born to 10 women with $\geq 10^5$ GBS colony-forming units/mL in their urine. Six of these women, but not the mother of the infected infant, received antepartum antibiotics. These studies vary widely with respect to definitions of significant bacteriuria, ranging from any GBS in the urine[135] to requiring two sequential urine cultures with $\geq 10^5$ organisms/mL,[136] but bacteriuria (even if urine obtained by bladder aspiration is sterile) may be an indication of heavy GBS colonization.[136] This dataset is very small, and these data may be skewed by selection or reporting bias, but the observation that 7 of 92 infants born to mothers with GBS bacteriuria in these prospective studies developed GBS infection suggests an attack rate of 76 (95% CI: 51–101) per 1000 such infants.

Sibling With GBS Infection

Although having had a previous infant with invasive GBS disease is accepted widely as placing a mother at high risk in subsequent pregnancies, only four instances have been reported in which neonatal GBS infection followed more than one pregnancy in the same mother.[137–139] We have seen other instances of this event, so it probably is not as unusual as is suggested by the rarity of reported cases. Women may remain colonized with the same strain of GBS for prolonged periods[140] and may fail to develop protective levels of type-specific serum antibodies despite long-term colonization.[140,141] It is likely that the risk in subsequent pregnancies is very high for women who have had a child with EOGBS disease, but this risk cannot be quantitated more precisely.

Multiple Gestation

Several reviews[1,17,30,34,36] and the 1992 AAP guidelines for prevention of group B streptococcal infection[15] state that the prevalence of neonatal GBS disease is increased in twins, but published data do not support this belief. The first suggestion of an increased risk in twin gestations was an incidental observation of twins concordant for disease in a patient sample collected for another purpose.[142] The prevalence of infection in twins <2500 g birth weight (3 of 56) was not significantly different from that (7 of 603) in LBW singletons ($P > .05$ by both the G test of independence[51] and χ^2 test with Yate's continuity correction)[143] and there were no cases of GBS infection in twins of birth weight ≥2500 g. Edwards et al[144] described 5 sets of twins and 1 set of triplets in which at least 1 infant had EOGBS disease, but provided no comparison with singleton pregnancies. In a survey of GBS infections in Denmark,[104] univariate analysis noted a relative risk of 6.9 for twins compared with singletons. Of the 6 twins with EOGBS disease, 5 were LBW, a group for which the relative risk in the same study was 14.8, thus apparent increased risk for twins in that population is attributable to the expected high prevalence of LBW in multiple gestations. A geographic cohort of >44 000 births in Western Canada exhibited no association between multiple gestation and EOGBS infection ($P > .25$).[145] Among 848 products of multiple gestation in that study, no culture-positive EOGBS case was observed; both cases of presumed GBS infection (infants with positive urine latex agglutination tests) occurred in preterm (<35 weeks) infants with PROM. A recent case-control study failed to show any differential risk for twins (OR 95% CI: .24–2.71).[111] Other large population studies have also failed to detect an association.[3,107] Multiple gestation is not an independent risk factor for GBS infection.

However, if 1 neonate from a multiple gestation has GBS infection, the risk of disease in the other(s) may be substantial. Concordance of EOGBS disease has been reported in twins,[142,144] triplets,[144] and quintuplets.[146] Pass[142] reported EOGBS sepsis in 1 of 2 twins of index cases. In Edwards' series,[144] 2 of the 5 twins of index cases with early-onset sepsis and 2 of 6 twins of index cases with late-onset infections also developed GBS disease. In the triplets described in their report, 1 infant had EOGBS disease, 1 infant died at 2 hours of age (no bacterial cultures were obtained), and 1 infant remained well. Although these reports may be skewed by preferential reporting of concordant cases, neonatal GBS colonization and lack of protective maternal antibody are likely to be the same in all products of a multiple birth. These data suggest that the prevalence of GBS infection

may exceed 40% among other members of a multiple birth group in which 1 infant has EOGBS disease.

Other Factors

Race or ethnicity,[3,111] maternal age,[3,111] internal monitoring for >12 hours,[88] meconium staining,[107] asphyxia,[4] and fetal acidosis,[147] and other factors also may be associated with increased risk. These variables may be covariant with GBS colonization, gestational age at delivery, duration of ruptured membranes, or other factors; therefore, their independent contributions are not delineated readily. Several of these factors are only apparent at or after delivery, and, therefore, are of little utility to strategies for prevention.

DISCUSSION

This review of the literature allows classification of clinical risk factors into two groups: factors that are associated with very high attack rates (>50/1000 live births) but that are relatively rare, and other factors that are more prevalent yet associated with less extreme increases in risk (attack rates of 10–25/1000). Clinical factors associated with the highest risks are shown in Table 9. Data related to maternal GBS bacteriuria or an affected sibling or twin are not sufficient for calculation of ORs, but the apparent very high attack rates are appropriately cause for serious concern about these infants. The consensus recommendation for intrapartum prophylaxis of their mothers[23] is well-justified, and evaluation and treatment of the infants is probably also appropriate, at least until infection is excluded by a period of observation and negative cultures. The apparently very high risk in infants born to GBS-colonized mothers with preterm premature rupture of membranes justifies empiric treatment of these women at least until cultures have excluded vaginal colonization with GBS. Infants born to women with chorioamnionitis are at high risk for neonatal sepsis, attributable to both GBS and other organisms, and may be uniquely at risk for infection even after maternal intrapartum antibiotic therapy. We concur with Merenstein's recommendation that infants born to women with chorioamnionitis should have a complete evaluation for GBS sepsis and receive empirical treatment until infection is ruled out, regardless of whether their mothers received intrapartum treatment.[130]

TABLE 9. Risk Factors Associated With Very High Early-onset GBS Attack Rates

Clinical Risk Factor	Approximate Prevalence (%)	Approximate Attack Rate (%)	References
Twin with early-onset GBS disease	≪.1	40	142, 144, 146
PPROM* in a GBS-colonized mother	<.5	33–50	114, 115
Chorioamnionitis	1–4	6–20	88, 118, 125–128
GBS bacteriuria during current pregnancy	2.5	8	134–136
Sibling with early-onset GBS disease	<1	Unknown	137–139

* PPROM, preterm (<37 weeks) premature (before onset of labor) rupture of membranes.

Estimates for the prevalence of and ORs for clinical factors associated with less extreme apparent risk are summarized in Table 10. These parameters were used to calculate the expected probability of a GBS case among patients with each risk factor (the positive predictive value of the observation). From this probability, the sensitivity, specificity, and predictive values, and the proportion of cases associated with each of the risk factors identified by this review have been calculated (Table 10), based on a presumed population attack rate of 3/1000 live births. For populations with different attack rates, the estimated risk-specific attack rates can be adjusted proportionately. This risk allocation indicates that the most sensitive and specific tool for identification of infants who are at risk for EOGBS infection is a maternal vaginal culture obtained at the time of delivery. This test identifies a group that includes <15% of all parturients, only 2% of whom have GBS infection but who account for >97% of all infants who develop EOGBS disease. However, the delay in availability of these results make this test useless for selection of patients for preventive interventions. Screening with rectovaginal cultures at 36 weeks gestation identifies just over 20% of the population that includes 57% of EOGBS cases, missing 35% of the GBS cases because the women deliver before screening is scheduled. Screening at 28 weeks reduces the proportion of women who deliver before screening to <1%, but this gain is largely offset by the lower predictive values associated with earlier screening. That strategy identifies 23% of the population that includes only 65% of infants with EOGBS. Currently, the best available method for screening for maternal vaginal colonization is the Strep B OIA, which can be used for nearly all deliveries (except deliveries that are precipitous or that occur before arrival in the obstetrical suite). That test identifies a group of <17% of all mothers that includes >75% of infants with early-onset disease, thus this should be the preferred method for ascertainment of risk based on maternal vaginal colonization at delivery. Of the other clinical risk factors, only PROM and the combination of intrapartum fever, PROM, and birth weight ≤2500 g identify subpopulations (of 12.5% and 18.3% of the population, respectively) that include >50% of the infants who will have EOGBS disease. Although GBS infection is expected in <2% of infants with any one of these risk factors, they may identify mothers whose infants are at sufficient risk to justify preventive interventions.

The CDC has recommended two strategies for identifying women whose infants are at risk for EOGBS sepsis and advocates intrapartum antibiotic prophylaxis for these at-risk populations.[23] These recommendations are based on a projected reduction in the EOGBS attack rate by 86% with application of the more aggressive of these approaches. The risk analysis presented in Table 10 indicates that no group that is defined by a single risk identifier includes ≥85% of the infants ex-

TABLE 10. Allocation of Risk for Early-onset GBS Infections

Risk Indicator	Risk Status	OR	Prevalence (%)	% of GBS Cases	Positive Predictive Value*	Negative Predictive Value	Sensitivity	Specificity
Maternal vaginal culture at delivery	GBS−	1.00	85.3	2.7	.0001			
	Light GBS	97.1	4.1	13.2	.0095	.9735	.1319	.9588
	Heavy GBS	247	10.5	83.9	.0239	.9905	.8398	.8968
	All GBS+	204	14.7	97.3	.0199	.9999	.9727	.8556
Maternal rectovaginal culture at 28 wk	GBS−	1.00	76.6	22.2	.0009			
	GBS+	9.64	22.6	65.8	.0087	.9987	.6586†	.7754†
	Already delivered	51.7	.8	11.9	.0448			
Maternal rectovaginal culture at 36 wk	GBS−	1.00	69.3	6.5	.0003			
	GBS+	26.7	20.4	58.0	.0085	.9984	.5805†	.7969†
	Already delivered	32.9	10.3	35.5	.0103			
Maternal vaginal Strep B OIA at delivery	GBS−	1.00	83.4	24.9	.0009			
	GBS+	15.4	16.6	75.1	.0137	.9991	.7511	.8359
Birth weight	500–1000 g	24.8	.6	10.6	.0510	.9909	.3143	.9276
	1001–1500 g	7.45	.8	4.3	.0159	.9882	.1280	.9019
	1501–2000 g	8.16	1.3	7.6	.0174	.9887	.2238	.8433
	2000–2500 g	3.96	3.4	9.8	.0085	.9851	.2890	.5835
	>2500 g	1.00	93.8	67.7	.0022			
	All ≤2500 g	7.33	6.2	32.3	.0157	.9978	.3227	.9390
Prematurity	Term (≥37 wks)	1.00	89.7	64.5	.0022			
	Preterm (<37 wks)	4.83	10.3	35.5	.0103	.9978	.3550	.8978
	<28 wks	21.7	.8	11.9	.0448	.9973	.1195	.9923
	28–30 wks	10.0	.9	6.4	.0212	.9972	.0636	.9912
	31–33 wks	4.65	2.1	7.0	.0100	.9971	.0697	.9791
	34–36 wks	2.19	6.5	10.2	.0047	.9971	.1023	.9351
Prematurity and birth weight	Term or >2500 g	1.00	96.1	69.1	.0022			
	<37 wk ≤2500 g	11.4	3.9	30.9	.0240	.9978	.3087	.9622
Prolonged rupture of membranes	≤18 h	1.00	87.5	49.3	.0017			
	>18 h	7.28	12.5	50.7	.0122	.9983	.5072	.8761
Intrapartum fever	≤37.5°C	1.00	94.3	80.4	.0026			
	>37.5°C	4.05	5.7	19.6	.0103	.9974	.1963	.9432
Chorioamnionitis	Absent	1.00	90.0	58.7	.0020			
	Present	6.43	10.0	41.3	.0124	.9980	.4132	.9013
Intrapartum fever, PROM, or prematurity	All absent	1.00	82.9	33.5	.0012			
	One or more present	9.74	17.1	66.5	.0117	.9988	.6650	.8307
Intrapartum fever or PROM in term infants	Both absent	1.00	82.9	33.5	.0012			
	One or both present	11.5	6.8	31.0	.0137	.9988	.3100	.8307

* The attack rate (cases of early-onset GBS infection per 1000 live births) in each group is the PPV × 1000.
† These sensitivity and specificity values are for all newborn infants, not just those available for screening at 28 or 36 wks, respectively.

pected to have invasive GBS disease, which would be required to achieve the efficacy target for prevention strategies that has been set implicitly by the recent CDC recommendations. The ideal risk ascertainment strategy would combine risk factors to identify a group including the greatest possible number of infants who will develop GBS disease within the smallest number of women who were determined to be at risk. Using two or more risk identifiers in sequence or combination is considered in a companion article.[148]

Despite the extensive literature relevant to ascertainment of risk for EOGBS, many questions remain unanswered. In contrast to the numerous studies of GBS disease, few studies have sought to identify correlates of risk for early-onset neonatal sepsis caused by other organisms, thus it is difficult or impossible to define conditions scientifically (other than chorioamnionitis) that should dictate use of broad-spectrum antimicrobial therapy. Although prematurity/LBW, intrapartum fever, and PROM each increase the risk for GBS infection, available data do not reveal threshold values for these factors, ie, gestational age <28 weeks, birth weight <1000 g, fever ≥40°C, or PROM >48 hours beyond which empirical treatment, rather than prophylactic interventions, might be necessary. The criteria for diagnosis of and risks associated with GBS bacteriuria need to be defined better, and the implications of diagnosis of GBS disease in a sibling or a twin should be quantitated in population-based studies. Because reduced attack rates resulting from effective preventive strategies may make it more difficult to answer such questions, systematic collection and publication of such information should be encouraged strongly.

ACKNOWLEDGMENTS

We thank Chad Hellig for abstracting demographic statistics from the 1992 California birth cohort data.

REFERENCES

1. Baker C, Edwards M. Group B streptococcal infections. In: Remington J, Klein J, eds. *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, PA: WB Saunders Co; 1995:980–1054
2. Zangwill KM, Schuchat A, Wenger JD. Group B streptococcal disease in the United States, 1990: report from a multistate active surveillance system. *MMWR CDC Surveillance Summary*. 1992;41:25–32
3. Schuchat A, Oxtoby M, Cochi S, et al. Population-based risk factors for neonatal group B streptococcal disease: results of a cohort study in metropolitan Atlanta. *J Infect Dis*. 1990;162:672–677
4. Yagupsky P, Menegus MA, Powell KR. The changing spectrum of group B streptococcal disease in infants: an eleven-year experience in a tertiary care hospital. *Pediatr Infect Dis J*. 1991;10:801–808
5. Weisman LE, Stoll BJ, Cruess DF, et al. Early-onset group B streptococcal sepsis: a current assessment. *J Pediatr*. 1992;121:428–433
6. Chin KC, Fitzhardinge PM. Sequelae of early-onset group B hemolytic streptococcal neonatal meningitis. *J Pediatr*. 1985;106:819–822
7. Edwards MS, Rench MA, Haffar AA, Murphy MA, Desmond MM, Baker CJ. Long-term sequelae of group B streptococcal meningitis in infants. *J Pediatr*. 1985;106:717–722
8. Wald ER, Bergman I, Taylor HG, Chiponis D, Porter C, Kubek K. Long-term outcome of group B streptococcal meningitis. *Pediatrics*. 1986;77:217–221
9. Faix RG, Donn SM. Association of septic shock caused by early-onset group B streptococcal sepsis and periventricular leukomalacia in the preterm infant. *Pediatrics*. 1985;76:415–419
10. Lannering B, Larsson LE, Rojas J, Stahlman MT. Early onset group B streptococcal disease: seven year experience and clinical scoring system. *Acta Paediatr Scand*. 1983;72:597–602
11. Gladstone IM, Ehrenkranz RA, Edberg SC, Baltimore RS. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. *Pediatr Infect Dis J*. 1990;9:819–825
12. Institute of Medicine. Prospects for immunizing against Streptococcus group B. In: *New Vaccine Development: Establishing Priorities. Diseases of Importance in the United States, I*. Washington, DC: National Academy Press; 1985:424–439
13. Hall RT, Barnes W, Krishnan L, et al. Antibiotic treatment of parturient women colonized with group B streptococci. *Am J Obstet Gynecol*. 1976;124:630–634
14. Group B streptococcal infections in pregnancy. ACOG Technical Bulletin. No 170, July 1992. *Int J Gynaecol Obstet*. 1993;42:55–59
15. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidelines for prevention of group B streptococcal (GBS) infection by chemoprophylaxis. *Pediatrics*. 1992;90:775–778
16. Hankins GV, Chalas E. Group B streptococcal infections in pregnancy: ACOG's recommendations. *ACOG Newslett*. 1993;37:2
17. Katz VL. Management of group B streptococcal disease in pregnancy. *Clin Obstet Gynecol*. 1993;36:832–842
18. Larsen JW, Dooley SL. Group B streptococcal infections: an obstetrical viewpoint. *Pediatrics*. 1993;91:148–149
19. American College of Obstetrics and Gynecology. Survey shows continued confusion over management of GBS in pregnancy. *ACOG Newslett*. 1994;38:1,10
20. Landon MB, Harger J, McNellis D, Mercer B, Thom EA. Prevention of neonatal group B streptococcal infection. *Obstet Gynecol*. 1994;84: 460–462
21. Mercer BM, Ramsey RD, Sibai BM. Prenatal screening for group B Streptococcus. II. Impact of antepartum screening and prophylaxis on neonatal care. *Am J Obstet Gynecol*. 1995;173:842–846
22. Mercer BM, Ramsey RD, Sibai BM. Prenatal screening for group B Streptococcus. I. Impact of antepartum screening on antenatal prophylaxis and intrapartum care. *Am J Obstet Gynecol*. 1995;173:837–841
23. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: a public health perspective. *MMWR Morb Mortal Wkly Rep*. 1996;45(No RR-7):1–24
24. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. ACOG committee opinion. Prevention of early-onset group B streptococcal disease in newborns. No 173, June 1996. *Int J Gynaecol Obstet*. 1996;54:197–205
25. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. *Pediatrics*. 1997;99:489–496
26. Gotoff SP, Boyer KM. Prevention of early-onset neonatal group B streptococcal disease. *Pediatrics*. 1997;99:866–869
27. Halsey NA, Schuchat A, Oh W, Baker CJ. The 1997 AAP guidelines for prevention of early-onset group B streptococcal disease. *Pediatrics*. 1997;100:383–384
28. Minkoff H, Mead P. An obstetric approach to the prevention of early-onset group B β-hemolytic streptococcal sepsis. *Am J Obstet Gynecol*. 1986;154:973–977
29. Gotoff SP, Boyer KM. Prevention of group B streptococcal early onset sepsis: 1989. *Pediatr Infect Dis J*. 1989;8:268–270
30. Noya FJ, Baker CJ. Prevention of group B streptococcal infection. *Infect Dis Clin North Am*. 1992;6:41–55
31. Jeffery HE, McIntosh ED. Antepartum screening and non-selective intrapartum chemoprophylaxis for group B streptococcus. *Aust N Z J Obstet Gynaecol*. 1994;34:14–19
32. Easmon CS. What is the risk of β-haemolytic streptococcal infection in obstetrics?: discussion paper. *J R Soc Med*. 1984;77:302–308
33. Dashefsky B, Wald ER, Green M. Prevention of early-onset group B streptococcal sepsis. *J Pediatr*. 1988;112:1039–1042
34. Steele RW. Control of neonatal group B streptococcal infection. *J R Soc Med*. 1993;86:712–715
35. Garland SM. Early onset neonatal group B streptococcus (GBS) infection: associated obstetric risk factors. *Aust N Z J Obstet Gynaecol*. 1991;31:117–118
36. Gilbert GL, Isaacs D, Burgess MA, et al. Prevention of neonatal group B streptococcal sepsis: is routine antenatal screening appropriate. *Aust N Z J Obstet Gynaecol*. 1995;35:120–126
37. Gibbs RS, Hall RT, Yow MD, McCracken GH, Nelson JD. Consensus: perinatal prophylaxis for group B streptococcal infection. *Pediatr Infect Dis J*. 1992;11:179–183
38. Allen UD, Navas L, King SM. Effectiveness of intrapartum penicillin prophylaxis in preventing early-onset group B streptococcal infection: results of a meta-analysis. *Can Med Assoc J*. 1993;149:1659–1665
39. Ohlsson A, Myhr TL. Intrapartum penicillin prophylaxis of early-onset streptococcal infection. *Can Med Assoc J*. 1994;150:1197–1198. Letter
40. Mohle-Boetani JC, Schuchat A, Plikaytis BD, Smith JD, Broome CV. Comparison of prevention strategies for neonatal group B streptococcal infection: a population-based economic analysis. *JAMA*. 1993;270: 1442–1448
41. Strickland DM, Yeomans ER, Hankins GD. Cost-effectiveness of intrapartum screening and treatment for maternal group B streptococci colonization. *Am J Obstet Gynecol*. 1990;163:4–8
42. Garland SM, Kelly N. Early-onset neonatal group B streptococcal sepsis: economics of various prevention strategies. *Med J Aust*. 1995; 162:413–417
43. Yancey MK, Duff P. An analysis of the cost-effectiveness of selected protocols for the prevention of neonatal group B streptococcal infection. *Obstet Gynecol*. 1994;83:367–371
44. Rouse DJ, Goldenberg RL, Cliver SP, Cutter GR, Mennemeyer ST, Fargason CA. Strategies for the prevention of early-onset neonatal group B streptococcal sepsis: a decision analysis. *Obstet Gynecol*. 1994; 83:483–494
45. Schuchat A, Wenger JD. Epidemiology of group B streptococcal disease: risk factors, prevention strategies, and vaccine development. *Epidemiol Rev*. 1994;16:374–402
46. Public Health Service. *Vital Statistics of the United States 1991*. Vol 1. Hyattsville, MD: United States Department of Health and Human Services, National Center for Health Statistics; 1995:281
47. Fleiss JL. *Statistical Methods for Rates and Proportions*. New York, NY: John Wiley and Sons; 1981:92
48. Armitage P, Berry G. *Statistical Methods in Medical Research*. London, UK: Blackwell Science; 1994:508–519
49. Sokol R, Rohlf F. *Biometry*. New York, NY: WH Freeman; 1995:71–81
50. Glantz S. *Primer of Biostatistics*. New York, NY: McGraw-Hill; 1992: 114–121
51. Sokol R, Rohlf F. *Biometry*. New York, NY: WH Freeman; 1995;698: 724–760
52. Fleiss JL. *Statistical Methods for Rates and Proportions*. New York, NY: John Wiley and Sons; 1981:147–149
53. Murray JF, Bergus GR. Using data from epidemiologic studies to revise probabilities. *Primary Care: Clinics in Office Practice*. 1995;22:247–259
54. Armitage P, Berry G. *Statistical Methods in Medical Research*. London, UK: Blackwell Science; 1994:522–525
55. Boyer KM, Gadzala CA, Burd LI, Fisher DE, Paton JB, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B strepto-

coccal early-onset disease. I. Epidemiologic rationale. *J Infect Dis*. 1983; 148:795–801
56. Pass MA, Gray BM, Khare S, Dillon HC. Prospective studies of group B streptococcal infections in infants. *J Pediatr*. 1979;95:437–443
57. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. *J Infect Dis*. 1983;148:802–809
58. Merenstein GB, Todd WA, Brown G, Yost CC, Luzier T. Group B β-hemolytic streptococcus: randomized controlled treatment study at term. *Obstet Gynecol*. 1980;55:315–318
59. Allardice JG, Baskett TF, Seshia MM, Bowman N, Malazdrewicz R. Perinatal group B streptococcal colonization and infection. *Am J Obstet Gynecol*. 1982;142:617–620
60. Morales WJ, Lim DV, Walsh AF. Prevention of neonatal group B streptococcal sepsis by the use of a rapid screening test and selective intrapartum chemoprophylaxis. *Am J Obstet Gynecol*. 1986;155:979–983
61. Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients. *Obstet Gynecol*. 1989;73:583–587
62. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med*. 1986;314:1665–1669
63. Matorras R, Garcia-Perea A, Omenaca F, Diez-Enciso M, Madero R, Usandizaga JA. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. *Eur J Obstet Gynecol Reprod Biol*. 1991;40:57–62
64. Wiswell TE, Hachey WE. Multiple site blood cultures in the initial evaluation for neonatal sepsis during the first week of life. *Pediatr Infect Dis J*. 1991;10:365–369
65. Kellogg JA, Ferrentino FL, Goodstein MH, Liss J, Shapiro SL, Bankert DA. Frequency of low level bacteremia in infants from birth to two months of age. *Pediatr Infect Dis J*. 1997;16:381–385
66. Cumming CG, Ross PW, Lough H. Optimal methods for the isolation of groups A, B, C and G streptococci. *J Laryngol Otol*. 1981;95:377–384
67. Baker CJ, Clark DJ, Barrett FF. Selective broth medium for isolation of group B streptococci. *Appl Microbiol*. 1973;26:884–885
68. Szilagyi G, Mayer E, Eidelman AI. Rapid isolation and identification of group B streptococci from selective broth medium by slide co-agglutination test. *J Clin Microbiol*. 1978;8:410–412
69. Gray BM, Pass MA, Dillon HC. Laboratory and field evaluation of selective media for isolation of group A streptococci. *J Clin Microbiol*. 1979;9:466–470
70. Fenton LJ, Harper MH. Evaluation of colistin and nalidixic acid in Todd-Hewitt broth for selective isolation of group B streptocci. *J Clin Microbiol*. 1979;9:167–169
71. Baker CJ, Goroff DK, Alpert S, et al. Vaginal colonization with group B streptococcus: a study in college women. *J Infect Dis*. 1977;135:392–397
72. Easmon CSF, Hastings MJG, Neill J, Bloxham B, Rivers RPA. Is group B streptococcal screening during pregnancy justified? *Br J Obstet Gynaecol*. 1985;92:197–201
73. Persson KM, Forsgren A. Evaluation of culture methods for isolation of group B streptococci. *Diagn Microbiol Infect Dis*. 1987;6:175–177
74. Kontnick CM, Edberg SC. Direct detection of group B streptococci from vaginal specimens compared with quantitative culture. *J Clin Microbiol*. 1990;28:336–339
75. Clark P, Armer T, Duff P, Davidson K. Assessment of a rapid latex agglutination test for group B streptococcal colonization of the genital tract. *Obstet Gynecol*. 1992;79:358–363
76. Carroll KC, Ballou D, Varner M, Chun H, Traver R, Salyer J. Rapid detection of group B streptococcal colonization of the genital tract by a commercial optical immunoassay. *Eur J Clin Microbiol Infect Dis*. 1996;15:206–210
77. MacDonald SW, Manuel FR, Embil JA. Localization of group B β-hemolytic streptococci in the female urogenital tract. *Am J Obstet Gynecol*. 1979;133:57–59
78. Badri MS, Zawaneh S, Cruz AC, et al. Rectal colonization with group B *Streptococcus*: relation to vaginal colonization of pregnant women. *J Infect Dis*. 1977;135:308–312
79. Dillon HC, Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. *J Infect Dis*. 1982;145: 794–799
80. Anthony BF, Okada DM, Hobel CJ. Epidemiology of group B Streptococcus: longitudinal observations during pregnancy. *J Infect Dis*. 1978;137:524–530
81. Yow MD, Leeds LJ, Thompson PK, Mason EO, Clark DJ, Beachler CW. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. I. Colonization studies. *Am J Obstet Gynecol*. 1980;137:34–38
82. Matorras R, Garcia-Perea A, Usandizaga JA, Omenaca F. Natural transmission of group B Streptococcus during delivery. *Int J Gynaecol Obstet*. 1989;30:99–103
83. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy: vaginal Infections and Prematurity Study Group. *Obstet Gynecol*. 1991;77:604–610
84. Ferrieri P, Cleary PP, Seeds AE. Epidemiology of group-B streptococcal carriage in pregnant women and newborn infants. *J Med Microbiol*. 1977;10:103–114
85. Ancona RJ, Ferrieri P, Williams PP. Maternal factors that enhance the acquisition of group-B streptococci by newborn infants. *J Med Microbiol*. 1980;13:273–280
86. Dillon HC, Khare S, Gray BM. Group B streptococcal carriage and disease: a 6-year prospective study. *J Pediatr*. 1987;110:31–36
87. Regan JA, Klebanoff MA, Nugent RP, et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. *Am J Obstet Gynecol*. 1996;174:1354–1360
88. Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. *Obstet Gynecol*. 1996;87:188–194
89. Anthony BF, Okada DM, Hobel CJ. Epidemiology of the group B streptococcus: maternal and nosocomial sources for infant acquisitions. *J Pediatr*. 1979;95:431–436
90. Armer T, Clark P, Duff P, Saravanos K. Rapid intrapartum detection of group B streptococcal colonization with an enzyme immunoassay. *Am J Obstet Gynecol*. 1993;168:39–43
91. Biostar. Package insert for Strep B OIA test kit; 1995
92. Park CH, Ruprai D, Vandel NM, Hixon DL, Mecklenberg FE. Rapid detection of group B streptococcal antigen from vaginal specimens using a new optical immunoassay technique. *Diagn Microbiol Infect Dis*. 1996;24:125–128
93. Anthony BF, Eisenstadt R, Carter J, Kim KS, Hobel CJ. Genital and intestinal carriage of group B streptococci during pregnancy. *J Infect Dis*. 1981;143:761–766
94. Islam AK, Thomas E. Faecal carriage of group B streptococci. *J Clin Pathol*. 1980;33:1006–1008
95. Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. *Obstet Gynecol*. 1996;88: 811–815
96. Committee on Obstetric Practice. Prevention of early-onset group B streptococcal disease in newborns. *ACOG Committee Opinion*. 1996;173: 1–8
97. Cardwell MS. Preventing perinatal early-onset group B streptococcal infections. The new standard of care. *J Leg Med*. 1997;18:511–519
98. Deutchman M. Thoughts on the prevention of neonatal group B streptococcal infection. *Am Fam Physician*. 1998;57:2602, 2605–2606. Editorial comment
99. Prevention of neonatal group B streptococcal sepsis: is routine antenatal screening appropriate. *Aust N Z J Obstet Gynaecol*. 1995;35: 120–121. Editorial comment
100. Baker CJ. Inadequacy of rapid immunoassays for intrapartum detection of group B streptococcal carriers. *Obstet Gynecol*. 1996;88:51–55
101. Tseng PI, Kandall SR. Group B streptococcal disease in neonates and infants. *N Y State J Med*. 1974;74:2169–2173
102. Quirante J, Ceballos R, Cassady G. Group B β-hemolytic streptococcal infection in the newborn. I. Early onset infection. *Am J Dis Child*. 1974;128:659–665
103. Baker CJ. Early onset group B streptococcal disease. *J Pediatr*. 1978;93: 124–125
104. Carstensen H, Henrichsen J, Jepsen OB. A national survey of severe group B streptococcal infections in neonates and young infants in Denmark, 1978–83. *Acta Paediatr Scand*. 1985;74:934–941
105. Stewardson-Krieger PB, Gotoff SP. Risk factors in early-onset neonatal group B streptococcal infections. *Infection*. 1978;6:50–53
106. Cochi SL, Feldman RA. Estimating national incidence of group B streptococcal disease: the effect of adjusting for birth weight. *Pediatr Infect Dis*. 1983;2:414–415. Letter
107. Spaans WA, Knox AJ, Koya HB, Mantell CD. Risk factors for neonatal infection. *Aust N Z J Obstet Gynaecol*. 1990;30:327–330
108. Romero R, Mazor M. Infection and preterm labor. *Clin Obstet Gynecol*. 1988;31:553–584
109. McLaren RA, Chauhan SP, Gross TL. Intrapartum factors in early-onset group B streptococcal sepsis in term neonates: a case-control study. *Am J Obstet Gynecol*. 1996;174:1934–1940
110. Matorras R, Garcia Perea A, Omenaca F, Usandizaga JA, Nieto A, Herruzo R. Group B streptococcus and premature rupture of membranes and preterm delivery. *Gynecol Obstet Invest*. 1989;27:14–18
111. Schuchat A, Deaver-Robinson K, Plikaytis BD, Zangwill KM, Mohle-

Boetani J, Wenger JD. Multistate case-control study of maternal risk factors for neonatal group B streptococcal disease. The Active Surveillance Study Group. *Pediatr Infect Dis J*. 1994;13:623–629
112. Adams WG, Kinney JS, Schuchat A, et al. Outbreak of early onset group B streptococcal sepsis. *Pediatr Infect Dis J*. 1993;12:565–570
113. McGregor JA, French JI. Use of antibiotics for preterm premature rupture of membranes. Rationales and results. *Obstet Gynecol Clin North Am*. 1992;19:327–338
114. Morales WJ, Angel JL, O'Brien WF, Knuppel RA. Use of ampicillin and corticosteroids in premature rupture of membranes: a randomized study. *Obstet Gynecol*. 1989;73:721–726
115. Newton ER, Clark M. Group B streptococcus and preterm rupture of membranes. *Obstet Gynecol*. 1988;71:198–202
116. Cimolai N, Roscoe DL. Contemporary context for early-onset group B streptococcal sepsis of the newborn. *Am J Perinatol*. 1995;12:46–49
117. Churgay CA, Smith MA, Blok B. Maternal fever during labor: what does it mean? *J Am Board Fam Pract*. 1994;7:14–24
118. Mecredy RL, Wiswell TE, Hume RF. Outcome of term gestation neonates whose mothers received intrapartum antibiotics for suspected chorioamnionitis. *Am J Perinatol*. 1993;10:365–368
119. Fusi L, Steer PJ, Maresh MJ, Beard RW. Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet*. 1989;1:1250–1252
120. Camann WR, Hortvet LA, Hughes N, Bader AM, Datta S. Maternal temperature regulation during extradural analgesia for labour. *Br J Anaesth*. 1991;67:565–568
121. Macaulay JH, Randall NR, Bond K, Steer PJ. Continuous monitoring of fetal temperature by noninvasive probe and its relationship to maternal temperature, fetal heart rate, and cord arterial oxygen and pH. *Obstet Gynecol*. 1992;79:469–474
122. Vinson DC, Thomas R, Kiser T. Association between epidural analgesia during labor and fever. *J Fam Pract*. 1993;36:617–622
123. Herbst A, Wolner-Hanssen P, Ingemarsson I. Risk factors for fever in labor. *Obstet Gynecol*. 1995;86:790–794
124. Lieberman E, Lang JM, Frigoletto F, Richardson DK, Ringer SA, Cohen A. Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation. *Pediatrics*. 1997;99:415–419
125. Yoder PR, Gibbs RS, Blanco JD, Castaneda YS, St. Clair PJ. A prospective, controlled study of maternal and perinatal outcome after intraamniotic infection at term. *Am J Obstet Gynecol*. 1983;145:695–701
126. Sperling RS, Ramamurthy RS, Gibbs RS. A comparison of intrapartum versus immediate postpartum treatment of intra-amniotic infection. *Obstet Gynecol*. 1987;70:861–865
127. Gibbs RS, Dinsmoor MJ, Newton ER, Ramamurthy RS. A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. *Obstet Gynecol*. 1988;72:823–828
128. Gilstrap LC, Leveno KJ, Cox SM, Burris JS, Mashburn M, Rosenfeld CR. Intrapartum treatment of acute chorioamnionitis: impact on neonatal sepsis. *Am J Obstet Gynecol*. 1988;159:579–583
129. Ascher DP, Becker JA, Yoder BA, et al. Failure of intrapartum antibiotics to prevent culture-proved neonatal group B streptococcal sepsis. *J Perinatol*. 1993;13:212–216
130. Merenstein GB, Gibbs RE, Weisman LE. Failure of maternal chemoprophylaxis to prevent neonatal group B streptococcal sepsis. *Pediatr Res*. 1996;39:298A
131. Persson K, Bjerre B, Elfstrom L, Polberger S, Forsgren A. Group B streptococci at delivery: high count in urine increases risk for neonatal colonization. *Scand J Infect Dis*. 1986;18:525–531
132. Gerards LJ, Cats BP, Hoogkamp-Korstanje JA. Early neonatal group B streptococcal disease: degree of colonisation as an important determinant. *J Infect*. 1985;11:119–124
133. Liston TE, Harris RE, Foshee S, Null DM. Relationship of neonatal pneumonia to maternal urinary and neonatal isolates of group B streptococci. *South Med J*. 1979;72:1410–1412
134. Wood EG, Dillon HC. A prospective study of group B streptococcal bacteriuria in pregnancy. *Am J Obstet Gynecol*. 1981;140:515–520
135. Møller M, Thomsen AC, Borch K, Dinesen K, Zdravkovic M. Rupture of fetal membranes and premature delivery associated with group B streptococci in urine of pregnant women. *Lancet*. 1984;2:69–70
136. Persson K, Christensen KK, Christensen P, Forsgren A, Jorgensen C, Persson PH. Asymptomatic bacteriuria during pregnancy with special reference to group B streptococci. *Scand J Infect Dis*. 1985;17:195–199
137. Carstensen H, Christensen KK, Grennert L, Persson K, Polberger S. Early-onset neonatal group B streptococcal septicaemia in siblings. *J Infect*. 1988;17:201–204
138. Faxelius G, Bremme K, Kvist-Christensen K, Christensen P, Ringertz S. Neonatal septicemia due to group B streptococci: perinatal risk factors and outcome of subsequent pregnancies. *J Perinat Med*. 1988;16:423–430
139. Philipson EH, Herson VC. Intrapartum chemoprophylaxis for group B streptococcus infection to prevent neonatal disease: who should be treated? *Am J Perinatol*. 1996;13:487–490
140. Dykes AK, Christensen KK, Christensen P. Chronic carrier state in mothers of infants with group B streptococcal infections. *Obstet Gynecol*. 1985;66:84–88
141. Christensen KK, Dahlander K, Linden V, Svenningsen N, Christensen P. Obstetrical care in future pregnancies after fetal loss in group B streptococcal septicemia: a prevention program based on bacteriological and immunological follow-up. *Eur J Obstet Gynecol Reprod Biol*. 1981;12:143–150
142. Pass MA, Khare S, Dillon HC. Twin pregnancies: incidence of group B streptococcal colonization and disease. *J Pediatr*. 1980;97:635–637
143. Glantz S. *Primer of Biostatistics*. New York, NY: McGraw-Hill; 1992:130–138
144. Edwards MS, Jackson CV, Baker CJ. Increased risk of group B streptococcal disease in twins. *JAMA*. 1981;245:2044–2046
145. Cimolai N. Multiple gestation is not a risk factor for early-onset group B streptococcal infection. *Clin Invest Med*. 1994;17:B80
146. Neri A, Wielunsky E, Henig E, Friedman S, Ovadia J. Group B streptococcus amnionitis with intact membranes associated with quintuplet delivery. *Eur J Obstet Gynecol Reprod Biol*. 1984;17:29–32
147. Montgomery DM, Stedman CM, Robichaux AG, Joyner JC, Scariano SM. Cord blood gas patterns identifying newborns at increased risk of group B streptococcal sepsis. *Obstet Gynecol*. 1991;78:774–777
148. Benitz WE, Gould JB, Druzin ML. Preventing early-onset group B streptococcal sepsis: strategy development using decision analysis. *Pediatrics*. 1999;103(6). URL: http://www.pediatrics.org/cgi/content/full/103/6/e76
149. Franciosi RA, Knostman JD, Zimmerman RA. Group B streptococcal neonatal and infant infections. *J Pediatr*. 1973;82:707–718
150. Siegel JD, Cushion NB. Prevention of early-onset group B streptococcal disease: another look at single-dose penicillin at birth. *Obstet Gynecol*. 1996;87:692–698
151. Pyati SP, Pildes RS, Ramamurthy RS, Jacobs N. Decreasing mortality in neonates with early-onset group B streptococcal infection: reality or artifact. *J Pediatr*. 1981;98:625–627
152. Baker CJ, Barrett FF. Transmission of group B streptococci among parturient women and their neonates. *J Pediatr*. 1973;83:919–925
153. Aber RC, Allen N, Howell JT, Wilkenson HW, Facklam RR. Nosocomial transmission of group B streptococci. *Pediatrics*. 1976;58:346–353
154. Payne NR, Burke BA, Day DL, Christenson PD, Thompson TR, Ferrieri P. Correlation of clinical and pathologic findings in early onset neonatal group B streptococcal infection with disease severity and prediction of outcome. *Pediatr Infect Dis J*. 1988;7:836–847
155. Opal SM, Cross A, Palmer M, Almazan R. Group B streptococcal sepsis in adults and infants. Contrasts and comparisons. *Arch Intern Med*. 1988;148:641–645
156. Siegel JD, McCracken GH, Threlkeld N, DePasse BM, Rosenfeld CR. Single-dose penicillin prophylaxis of neonatal group B streptococcal disease. *Lancet*. 1982;1:1426–1430
157. Patel DM, Leblanc MH, Morrison JC, et al. Postnatal penicillin prophylaxis and the incidence of group B streptococcal sepsis in neonates. *South Med J*. 1994;87:1117–1120
158. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. *Am J Obstet Gynecol*. 1981;139:512–515
159. Bobitt JR, Damato JD, Sakakini J. Perinatal complications in group B streptococcal carriers: a longitudinal study of prenatal patients. *Am J Obstet Gynecol*. 1985;151:711–717
160. Iams JD, O'Shaughnessy R. Antepartum versus intrapartum selective screening for maternal group B streptococcal colonization. *Am J Obstet Gynecol*. 1982;143:153–156
161. Yancey MK, Clark P, Armer T, Duff P. Use of a DNA probe for the rapid detection of group B streptococci in obstetric patients. *Obstet Gynecol*. 1993;81
162. Jones DE, Friedl EM, Kanarek KS, Williams JK, Lim DV. Rapid identification of pregnant women heavily colonized with group B streptococci. *J Clin Microbiol*. 1983;18:558–560
163. Beachler CW, Baker CJ, Kasper DL, Fleming DK, Webb BJ, Yow MD. Group B streptococcal colonization and antibody status in lower socioeconomic parturient women. *Am J Obstet Gynecol*. 1979;133:171–173
164. Gibbs RS, McDuffie RS, McNabb F, Fryer GE, Miyoshi T, Merenstein G. Neonatal group B streptococcal sepsis during 2 years of a universal screening program. *Obstet Gynecol*. 1994;84:496–500
165. Embil JA, Martin TR, Hansen NH, MacDonald SW. Group B β-haemolytic streptococci in the female genital tract: a study of four clinic populations. *Br J Obstet Gynaecol*. 1978;85:783–786

Risk Factors for Early-onset Group B Streptococcal Sepsis: Estimation of Odds Ratios by Critical Literature Review

William E. Benitz, Jeffrey B. Gould and Maurice L. Druzin

Pediatrics 1999;103;e77

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Risk Factors for Early-onset Group B Streptococcal Sepsis: Estimation of Odds Ratios by Critical Literature Review

William E. Benitz, Jeffrey B. Gould and Maurice L. Druzin

Pediatrics 1999;103;e77