

Risk factors for early-onset group B streptococcal disease in neonates: a population-based case-control study

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Abstract

Background: Infection with group B streptococcus (GBS) is a major cause of neonatal illness and death. We examined the antenatal and perinatal risk factors for early-onset GBS disease among neonates.

Methods: We identified cases by population-based surveillance in all microbiology laboratories serving Alberta. A case was defined as any instance of a positive sterile-site GBS culture in an infant born between 1993 and 1997 who was either less than 7 days old or stillborn after 20 weeks' gestation. We randomly selected controls from a computer-compiled list of all hospital births, including stillbirths after 20 weeks' gestation, in Alberta during the study period. To increase power, we chose 5 or 6 control infants born in the same year as each case infant. We reviewed hospital, prenatal clinic and physician health records and, between 1997 and 1999, conducted maternal interviews by telephone.

Results: There were no differences between the 90 cases and 489 controls in sociodemographic variables or in many reproductive and behavioural variables. Case infants were more likely than control infants to be of low birth weight (odds ratio [OR] 3.60, 95% confidence interval [CI] 1.68–7.65), to have been delivered preterm (OR 3.89, 95% CI 2.08–7.27), or to have a mother with amnionitis (OR 15.03, 95% CI 5.58–41.89), intrapartum fever (OR 4.65, 95% CI 2.48–8.69) or premature rupture of the membranes (OR 2.39, 95% CI 1.38–4.14). After adjustment for potential confounders, intrauterine fetal monitoring was associated with a more than 2-fold increase in the risk of neonatal GBS disease (OR 2.24, 95% CI 1.22–4.13).

Interpretation: Intrauterine fetal monitoring should be added to the list of risk factors in risk-based screening. Since many of the cases had no identifiable maternal risk factors, universal screening for GBS may be appropriate.

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Over the last 3 decades, infection with group B streptococcus (GBS) has emerged as a major cause of neonatal mortality and morbidity.¹⁻³ Before the implementation of preventive guidelines in 1994,⁴ Canadian rates of GBS infection ranged from 0.44 to 2.1 per 1000 live births,⁵ but they declined to 0.25 per 1000 by 1999.^{6,7} Risk

factors for GBS infection identified in the guidelines included preterm delivery, previous infant with GBS infection, GBS bacteriuria, intrapartum fever and premature rupture of the membranes (more than 18 hours before delivery).

Most studies identifying risk factors for neonatal GBS infection have lacked a comparison group, have been institution-based rather than population-based or have not included maternal interviews. A population-based study in the United States that used maternal interviews to identify risk factors did not use health record information and was limited by a high refusal rate (76%).^{2,8-11} Finally, overmatching may have masked some risk factors.¹²

The magnitude of risk associated with identified risk factors has varied considerably.^{9-11,13-15} For example, studies in Australia¹¹ and the United States¹⁵ found that 79% and 28%, respectively, of GBS-infected infants were preterm. Furthermore, many factors that may contribute to risk, such as sexual practices, use of prenatal medication, prenatal visits, vaginal examinations and intrauterine fetal monitoring, have not been thoroughly examined. A multistate US study¹⁶ suggested that almost 50% of all cases of GBS infection had none of the currently identified risk factors.

We examined known and new risk factors for GBS disease in all neonates in Alberta, using a population-based case-control study with multiple information sources.

Methods

We defined a case as any instance of a positive sterile-site GBS culture (e.g., of blood or cerebrospinal fluid) in an infant born between 1993 and 1997 who was either less than 7 days old or stillborn after 20 weeks' gestation.⁷ During this period, many obstetric care providers were following either the Canadian consensus guidelines¹⁷ or the American Academy of Pediatrics guidelines.¹⁸ We identified cases by population-based surveillance in all microbiology laboratories serving Alberta (1995 population 2.69 million and average annual birth rate 38 000¹⁹). The province is a mixed urban-rural region with defined geographic boundaries that are easily identified by the first character of the postal code (T). During the study period, there were 262 398 births (live and still). Laboratory audits were carried out 6 and 18 months after the start of the study and at completion of the study to confirm complete case ascertainment.⁷

We randomly selected controls from a computer-compiled list of all hospital births, including stillbirths after 20 weeks' gestation, in Alberta during the study period. To increase power, we chose 5 or 6 control infants born in the same year as each case infant.

We estimated the adequacy of prenatal care with the Kessner index,²⁰ which categorizes prenatal care as inadequate, intermediate or adequate on the basis of the timing of the initiation of prenatal care, gestational age at delivery and the number of visits for prenatal care. For the multivariable models, we used 2 categories: adequate (including intermediate) and inadequate.²¹ Amnionitis or chorioamnionitis was noted if diagnosed by the attending physician and mentioned in the health record. Our classification of chronic diseases was similar to that used in the Ontario Health Survey.²²

We developed the interview questionnaire using items from tested or standardized questionnaires, including the Behavioral Risk Factor Questionnaire,²³ the Pregnancy, Infection, and Nutrition study,²⁴ the National Alcohol and Drug Survey,²⁵ the Drug Use Screening Inventory-Revised²⁶ and the Canadian census. The questionnaire was translated into Chinese, French, Punjabi, Spanish, Urdu and Vietnamese. Techniques known to improve the validity of the responses and to minimize tendencies to provide socially desirable responses were used in questionnaire construction and the interviews.²⁷⁻³¹

All telephone interviews occurred between 1997 and 1999. We tried contact telephone numbers as many times as required to determine whether the mother could be reached. Verbal and then mailed written consent was obtained for the interview and for access to hospital and prenatal clinic records. Interviews were scheduled and forms coded and given to 2 interviewers trained in cognitive interviewing techniques and blind to disease status.³²⁻³⁴

Using pretested, standard data collection forms, 2 trained nurses reviewed hospital and prenatal clinic charts, mailed questionnaires to physicians' offices to collect prenatal information and verify some chart information, and made reminder telephone calls to encourage completion of the questionnaires.

All data were entered into a database and analyzed with statistical software. For univariate analyses and differences between cases and controls in categorical variables, we used the Z test or the χ^2 test for differences in proportions. For bivariate associations we used the χ^2 test (or Fisher's exact test when the expected values were less than 5) and calculated odds ratios (ORs) and Cornfield 95% confidence intervals (CIs).³⁵ We performed preliminary stratified analyses to inform variable selection for multivariate modelling and developed unconditional logistic regression models to examine important risk associations while adjusting for possible confounders, applying the Pearson χ^2 to evaluate the fit of the models.³⁶ Variables were included in the final model on the basis of their relations with the outcome in the bivariate and stratified analyses and after careful consideration of probable causal pathways. We examined the impact of collinearity by separately entering suspected collinear variables (e.g., duration of labour and premature rupture of the membranes, intrapartum fever and amnionitis) into the regression model. We based the power calculation on the prevalence of the exposure variable (the risk of preterm birth among GBS-positive infants versus all other Alberta infants): 6.8% in 1994 to 7.4% in 1996.³⁷ The study had an 80% or greater power to show a relative risk of 2.30 or more when the risk exposure rate in controls was 10% with $\alpha = 0.05$ and a relative risk of 3.00 or more when the risk exposure rate in controls was 5%.

The Conjoint Medical Research Ethics Board of the University of Calgary reviewed and approved the study protocol.

Results

Of the 92 cases of early-onset GBS disease identified between 1993 and 1997, a chart was not located for 1 case, and 1 mother refused to participate. Another 16 mothers (17.8% of the remaining 90 cases) consented to chart review but refused an interview or consented to an interview but could not be contacted for it; therefore, the chart was the only source of information in these cases. Of the 570 controls randomly selected, 11 were excluded by nonresidence. Of the remaining 559, 70 (12.5%) refused to participate and 6 (1.1%) refused only the interview; as well, 13 (2.7%) of those who consented to the interview could not be reached. Thus, the health records of 489 controls were reviewed, and 470 control interviews were conducted. All physician questionnaires were returned. Of the early-onset cases, excluding the 9 stillbirths, 11 (13.6%) resulted in death.

There were no differences between case and control infants in sociodemographic variables, including year of birth, sex, maternal residence, mother's marital status, socioeconomic status and year of interview (Table 1). Nor were there important differences in maternal reproductive history, including parity, previous spontaneous or therapeutic

Table 1: Characteristics of cases of early-onset infection with group B streptococcus (GBS) and control births in Alberta in 1993–1997

Variable	No. (and %)*	
	Cases <i>n</i> = 74	Controls <i>n</i> = 470
Year of birth		
1993	12 (16.2)	99 (21.1)
1994	15 (20.3)	69 (14.7)
1995	14 (18.9)	84 (17.9)
1996	19 (25.7)	140 (29.8)
1997	14 (18.9)	78 (16.6)
Male sex	40 (44.4)	255 (52.1)
Maternal residence		
Northern Alberta	38 (42.2)	252 (51.5)
Southern Alberta	52 (57.8)	237 (48.5)
Maternal marital status		
Legally married	64 (86.5)	377 (80.9)
Single, divorced, common-law relationship	10 (13.5)	89 (19.1)
Socioeconomic status		
Maternal education \leq 11 yr	12 (16.2)	52 (11.1)
Paternal education \leq 11 yr	14 (19.4)	79 (17.1)
Income < \$30 000/yr	11 (18.0)	88 (23.5)
Year of interview		
1997	21 (28.4)	150 (31.9)
1998	48 (64.9)	292 (62.1)
1999	5 (6.8)	28 (6.0)

*The denominators are the numbers of interviewed mothers; however, because of missing data, the numbers and percentages do not always reflect the stated totals. For sex and residence the denominators are 90 and 489, respectively, as other sources of information were used.

abortions, previous pregnancies or previous stillbirths, or in prevalence of maternal chronic disease (Table 2); notably, diabetes mellitus was present in 3 of 90 case mothers and 9 of the 489 control mothers, not a significant difference. However, significantly more case infants than control infants weighed less than 2500 g at birth, were born before 37 weeks' gestation or had a mother less than 20 years of age at the time of delivery (Table 2). In only 5 families (1 of 90 case families and 4 of 489 control families) had there previously been early-onset GBS infection in an infant. Although black race has been shown to be a risk factor for GBS infection in the United States, there were too few black patients (3) in this study to permit meaningful analysis.

From the interviews, neither oral contraceptive use nor intrauterine device (IUD) use was found to be associated with infant disease, whether measured as "ever used" or "duration of use" (data not shown). Sexual practices in the 6 months before pregnancy as well as during pregnancy, including frequency of intercourse and number of partners, were also not associated. Despite a high risk (OR = 6.41) associated with reported prostitution, this response was too rare for reliable estimation. Among substance use variables, including environmental exposure to tobacco smoke and use of tobacco and alcohol, no significant associations were found, but among those reporting extreme levels of substance use there were suggestive trends toward elevated risk. Neither over-the-counter nor prescription medication use was associated with GBS status (data not shown).

Rates of refusal to answer sensitive questions were generally very low. Among case families, there were no refusals. Among control families, the refusal rates were as follows: household income, 1.33%; oral contraceptive and IUD use, 0%; sexual practices, 0.2%–0.7%; smoking, alcohol and substance abuse, 0%.

Distinct patterns of risk were evident for certain antepartum and intrapartum variables (Table 3). Risk was not associated with adequacy of prenatal care, attendance at prenatal classes, antenatal screening for GBS, antibiotic use

(for either prophylaxis or therapy) either antenatally or during labour, or duration of labour. However, case status was strongly associated with indicators of active disease that were manifest during labour (premature rupture of the membranes [OR 2.39, 95% CI 1.38–4.14], maternal fever [OR 4.65, 95% CI 2.48–8.69] and amnionitis [OR 15.03, 95% CI 5.58–41.89]) as well as factors that represented consequences of disease (neonatal intubation [OR 3.42, 95% CI 1.65–7.06] and emergency cesarean section [OR 2.51, 95% CI 1.29–4.83]). The number of vaginal examinations and artificial rupture of the membranes showed no association with infant disease. However, the use of intrauterine fetal monitoring doubled the risk (OR 1.94, CI 1.09–3.42) in univariate analysis, and the magnitude of the association did not change (OR 2.24, 95% CI 1.22–4.13) after adjustment for premature rupture of the membranes, gestational age, maternal fever, number of prenatal visits, duration of labour and adequacy of prenatal care (Table 4). Of the 90 mothers of infants with GBS infection 42 had no identified risk factors.

Interpretation

Our study of neonatal GBS infection quantified risk factors in a population on the basis of multiple sources of information, including maternal interviews, caregiver questionnaires and chart reviews. We looked for both known and previously unknown factors. Intrauterine monitoring emerged as an independent risk factor. The hypothesis that monitoring increases the risk of GBS disease has biologic plausibility because there is a disruption of the skin barrier, which could allow GBS into the vascular system, as with herpetic infections.^{38–45}

An association between intrauterine monitoring and amnionitis has been reported,⁴⁶ but an association with early-onset GBS infection had not been confirmed owing to inadequacies of study design or sample size. In a multistate case-control study of 99 cases of early-onset GBS infection,

Table 2: Maternal and birth characteristics associated with early onset GBS infection

Variable	No. (and %)*		
	Cases <i>n</i> = 90	Controls <i>n</i> = 489	OR (and 95% CI)
Mother less than 20 yr old when infant born	9 (10.1)	22 (4.5)	2.38 (1.06–5.36)
Birth weight < 2500 g	14 (15.7)	24 (4.9)	3.60 (1.68–7.65)
Birth at < 37 wk gestation	22 (24.4)	37 (7.7)	3.89 (2.08–7.27)
No previous pregnancies	33 (37.1)	137 (28.0)	1.34 (0.81–2.21)
Previous spontaneous abortions	22 (24.7)	96 (19.6)	1.34 (0.76–2.35)
No previous births	40 (44.9)	179 (36.7)	1.41 (0.87–2.28)
Previous therapeutic abortions	3 (3.3)	39 (8.0)	0.40 (0.08–1.31)
Previous stillbirths	1 (1.1)	11 (2.2)	0.49 (0.01–3.48)
Chronic maternal disease	24 (28.8)	123 (26.9)	1.08 (0.63–1.85)

Note: OR = odds ratio, CI = confidence interval.

*Because of missing data, the numbers and percentages do not always reflect the stated totals.

internal monitor use was found to be associated with the disease by univariate but not multivariate analysis.² The study may have been affected by selection bias, since the families of 76% of identified cases did not participate in the study. Adams and colleagues⁹ also found that, after adjustment, use of an intrauterine pressure catheter did not appear to be a risk factor for early-onset GBS disease. However, this study investigated an outbreak of 23 cases over an 8-month period. Because such outbreaks are unusual, it is not known whether these cases differ from those not part of an outbreak. Bramer and coworkers⁸ identified internal monitoring as a risk factor for GBS disease. However, owing to the small number of GBS-positive cultures (19), the case definition was extended to positive cultures from non-sterile sites. Yancey and associates⁴⁷ found an association

between internal monitoring for more than 12 hours and neonatal sepsis; 10 of 15 cases of culture-proven sepsis were due to GBS.

So far, ours is the largest and most complete study to examine this association. Our positive finding suggests that intrauterine monitoring be added to the list of risk factors for neonatal GBS disease. The association was stable after adjustment for potential confounding factors — those that might have led to a higher likelihood of intrauterine monitoring (inadequate prenatal care, maternal fever or amnionitis, prolonged labour and preterm delivery) — and thus reinforced our conclusion that intrauterine monitoring is an independent risk factor. However, universal screening for GBS may be more appropriate than using risk factors, given the absence of risk factors in nearly half the cases.

Table 3: Antenatal and intrapartum events associated with early onset GBS infection

Variable	No. (and %)*		OR (and 95% CI)
	Cases <i>n</i> = 90	Controls <i>n</i> = 489	
Adequate (including intermediate) prenatal care†	86 (95.6)	467 (95.5)	0.99 (0.24–3.01)
No prenatal classes	51 (72.9)	239 (61.8)	1.66 (0.91–3.04)
No antenatal screening for GBS	45 (50.0)	206 (42.1)	1.37 (0.85–2.21)
Antenatal antibiotic prophylaxis or therapy	14 (15.9)	61 (12.5)	0.76 (0.39–1.50)
Intrapartum antibiotic prophylaxis or therapy	19 (21.1)	77 (15.7)	0.70 (0.39–1.27)
0 doses	73 (81.1)	412 (84.2)	0.80 (0.43–1.50)
1 dose	6 (6.7)	44 (9.0)	0.72 (0.24–1.78)
≥ 2 doses	11 (12.2)	33 (6.7)	0.52 (0.24–1.14)
At least 1 risk factor‡ and intrapartum antibiotic prophylaxis or therapy§			
0 doses	35 (72.9)	87 (70.2)	1.15 (0.51–2.58)
1 dose	3 (6.3)	17 (13.7)	0.42 (0.08–1.56)
≥ 2 doses	10 (20.8)	20 (16.1)	0.73 (0.29–1.85)
Maternal intrapartum fever (≥ 37.5°C)	23 (27.1)	36 (7.4)	4.65 (2.48–8.69)
Amnionitis	16 (18.0)	7 (1.4)	15.03 (5.58–41.89)
Rupture of membranes			
> 12 h before delivery	27 (32.5)	79 (16.8)	2.39 (1.38–4.14)
Artificial	36 (41.9)	228 (47.6)	0.79 (0.49–1.29)
Duration of labour (h)			
< 5	32 (37.6)	156 (35.7)	1.0
5–10	23 (27.0)	169 (38.7)	0.664 (0.372–1.18)
11–15	16 (18.8)	54 (12.4)	1.44 (0.735–2.84)
> 15	13 (15.3)	50 (11.4)	1.27 (0.616–260)
Three or fewer vaginal examinations	47 (55.3)	242 (51.9)	1.14 (0.70–1.87)
Intrauterine monitoring	23 (26.4)	76 (15.6)	1.94 (1.09–3.42)
Neonatal intubation	15 (16.7)	27 (5.5)	3.42 (1.65–7.06)
Emergency cesarean section v. vaginal delivery or elective cesarean section	17 (18.8)	42 (8.6)	2.51 (1.29–4.83)

*Because of missing data, the numbers and percentages do not always reflect the stated totals.

†According to the Kessner index, which is based on the timing of the initiation of prenatal care, gestational age at delivery and the number of visits for prenatal care.²⁰

‡Fever, amnionitis, premature rupture of the membranes or preterm birth.

§The denominator for the percentages is the number of births with at least 1 risk factor: 48 cases and 124 controls.

Frequency of vaginal examinations during labour was not associated with GBS disease, consistent with the theory that disruption of the skin or mucous membrane barrier, which occurs with intrauterine monitoring but not vaginal examination, is important in the pathogenesis of GBS disease. Univariate analyses have shown that 5 or more⁹ and 6 or more⁴⁸ vaginal examinations, respectively, increase the risk of GBS disease. However, it is difficult to compare these studies because of differences in and lack of information about variables that may affect the risk of disease, such as the timing (before v. after rupture of the membranes) and the frequency of the exams.

Unlike previous studies in the United States,^{2,15} our study demonstrated no relation between socioeconomic factors and GBS disease. This is most likely due to the universal availability of health care in Canada, without concern for ability to pay. The lack of association in our study between intrapartum antibiotic prophylaxis and case status is not surprising, because there was some screening and prophylaxis during the study period, as recommended by expert bodies. However, the 81.1% of cases in which there was no intrapartum antibiotic prophylaxis represents a large group of women who may need different methods of prevention, especially since nearly half (35 of 73) had an identifiable risk factor (fever, amnionitis, premature rupture of the membranes or preterm birth). This problem reinforces the difficulty of using a risk-based approach.^{49,50}

The random selection of controls minimized the risk of bias in this study. Refusal rates were low for both case and control groups. During the study period, the rates of low birth weight, preterm birth and neonatal death were very similar in the control group and the total neonatal population of Alberta (4.9% v. 5.9%, 7.6 v. 7.2% and 4.0 v. 4.2%, respectively).⁵¹ We minimized the risk of recall bias by conducting interviews at equal intervals from the time of birth for both case and control groups. The interviewers were blind to case status. No matching (other than frequency matching on year of birth) was used in this study. A matched case-control design has the risk of overmatching, which may hinder informative results or introduce confounding if the matching factor is correlated with exposure but not disease.¹²

Table 4: Results of multivariate logistic regression analysis of risk factors for GBS infection

Variable	OR (and 95% CI)
Intrauterine fetal monitoring	2.24 (1.22–4.13)
Rupture of membranes > 12 h before delivery	1.17 (0.63–2.17)
Birth at < 37 wk gestation	5.11 (2.54–10.28)
Maternal fever ($\geq 37.5^{\circ}\text{C}$)	2.64 (1.34–5.23)
Adequate prenatal care	0.91 (0.26–3.16)
Duration of labour > 10 h	1.84 (1.06–3.18)
Maternal amnionitis	1.66 (0.51–5.38)

*Model fit: Pearson $\chi^2 = 29.09$, $p = 0.82$.

A potential limitation of our study was use of the Kessner index to assess the adequacy of prenatal care. This index was designed primarily for a US population and has been criticized because it is heavily weighted toward the timing of the initiation of prenatal care, does not distinguish timing of initiation from poor subsequent frequency of visits and may inaccurately measure overall adequacy of care for term and post-term pregnancies.²⁰ However, there is currently no suitable alternative, and this index has recently been used by other investigators.²¹

In conclusion, this study of neonatal GBS disease in a Canadian population identified an association of elevated disease risk with intrauterine monitoring. No risk factor profile predicted all infant disease before labour, which suggests that universal screening may be more appropriate for prevention.

This article has been peer reviewed.

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Contributors: Dr. Adair contributed to the conception and design of the study, oversaw much of the running of the study and of the analyses, and co-drafted the paper and revised it for critical intellectual content. Ms. Kowalsky, Ms. Robertson and Ms. Mucenski contributed to the acquisition of data and the interviews and helped draft the paper. Mr. Quon contributed to the acquisition of data and helped draft the paper. Ms. Ma was responsible for most of the initial statistical analyses and helped with revision of the paper. Dr. Stoffman contributed to the design of the study and revision of the paper. Dr. McGeer contributed to the conception and design of the study and revision of the paper. Dr. Davies was the principal investigator, contributed to the conception and design of the study, was responsible for overall coordination of the study and analyses, co-drafted and revised the paper critically for important intellectual content, and was responsible for the final editing and submission. All authors approved the final version of the manuscript.

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