*Epidemiol. Infect.* (2013), **141**, 1089–1098. © Cambridge University Press 2012
doi:10.1017/S0950268812001598

# Group B streptococcal colonization and the risk of pre-eclampsia

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*Received 10 November 2011; Final revision 24 May 2012; Accepted 25 June 2012; first published online 20 July 2012*

## SUMMARY

To determine if there was an association between recto-vaginal group B streptococcus (GBS) colonization and pre-eclampsia, two cross-sectional studies were conducted using statewide hospital databases. The first study analysed data from the state of Florida, USA, and included 190 645 women who were discharged in 2001. This dataset was used to generate the hypothesis that GBS colonization is associated with pre-eclampsia. The second study tested the GBS hypothesis using the records of 577 153 women who delivered in 2004 or 2005 in Texas, USA. Adjusted odds ratios (aOR) for the outcome of pre-eclampsia comparing GBS-positive to GBS-negative women were calculated using logistic regression. The aOR for the association between GBS carriage and pre-eclampsia was 0·71 [95% confidence interval (CI) 0·65–0·77] in the Florida dataset. In the Texas dataset, the overall prevalence of GBS carriage was 14·1% while the overall prevalence of pre-eclampsia was 4·0%. GBS carriers were 31% less likely than non-carriers to have pre-eclampsia (aOR 0·69, 95% CI 0·66–0·72) in Texas. In two large statewide analyses, GBS carriage was inversely associated with pre-eclampsia. A sensitivity analysis revealed that misclassification of GBS status is not a likely explanation of our findings.

**Key words**: Group B streptococcus, maternal infection, pre-eclampsia, urinary tract infection.

## INTRODUCTION

Pre-eclampsia is a serious disorder of pregnancy characterized by new-onset hypertension and proteinuria [1]. This multisystem disorder affects about 5–7% of pregnancies [2]. Hypertensive disorders of pregnancy including pre-eclampsia are directly responsible for about 18% of maternal deaths in the USA [3]. Severe pre-eclampsia is associated with an elevated risk of several adverse outcomes such as placental abruption, renal failure, preterm delivery, and fetal death [3].

It has been hypothesized that maternal infection may be a risk factor for pre-eclampsia [4]. A recent meta-analysis conducted by Rustveld and colleagues

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A previous version of the abstract of this paper was presented at the 29th Annual Meeting of the Society for Maternal-Fetal Medicine, 30 January 2009, San Diego, California, USA.

found that any maternal bacterial or viral infection doubled the odds of pre-eclampsia [5]. Only one of the 16 studies [4] included in the meta-analysis by Rustveld *et al*. [5] addressed group B streptococcal infections and none addressed colonization by group B streptococci.

Group B streptococcus (GBS) is a major cause of severe neonatal infections [6]. Between 5% and 40% of pregnant women in the USA carry GBS in the vagina and/or rectum [7]. We could not identify any analytical epidemiological studies (e.g. cross-sectional, case-control, or cohort) of GBS recto-vaginal colonization as a possible risk factor for pre-eclampsia. The objective of our investigation was to determine if there was an association between GBS and the prevalence of pre-eclampsia in two large, statewide hospital discharge datasets. This GBS hypothesis was generated using a Florida dataset and tested using a Texas dataset. The results of both analyses are presented herein.

## METHODS

### Source population and inclusion criteria

Retrospective analyses were performed using hospital inpatient discharge data that were obtained from the Florida Agency for Health Care Administration (Tallahassee, Florida), and the Texas Department of State Health Services (Austin, Texas). The first dataset, representing women who delivered in Florida, was used to generate the hypothesis that GBS carriage was associated with prevalent pre-eclampsia. The second dataset from Texas was used to test this hypothesis.

The Florida database includes discharge summaries from all non-federal Florida hospitals except state tuberculosis and state mental health hospitals. After data are entered into this system, they are subjected to formatting and logic checks. The primary hospital submitting patient information must then certify the data are correct and verify the accuracy of a summary report before it is released by the Florida Agency for Health Care Administration. This dataset contains clinical and demographic information for patients who were hospitalized for at least 1 day and discharged from a reporting facility in the calendar year 2001 throughout the state of Florida. The principal discharge diagnosis and up to nine secondary discharge diagnoses were coded using the International Classification of Diseases, Ninth Revision – Clinical Modification (ICD-9-CM). Up to and including ten procedures that were performed during the hospital stay were recorded in this dataset using ICD-9-CM procedure codes.

The Texas database contained information from all state-licensed hospitals except those that are exempt from reporting to the Texas Health Care Information Council. According to the data user manual:

> Exempt hospitals include those located in a county with a population of less than 35 000, or those located in a county with a population more than 35 000 and with fewer than 100 licensed hospital beds and not located in an area that is delineated as an urbanized area by the United States Bureau of the Census.

Hospitals that do not seek insurance payment or government reimbursement are also exempt from the reporting requirement.

Both Texas public use and Texas research data were used in this study. The Texas dataset contained clinical and demographic information for patients who were discharged in calendar years 2004 and/or 2005. The principal diagnosis and up to 24 secondary diagnoses were evaluated in our study. These variables were coded using ICD-9-CM. Up to and including 25 procedures (a principal procedure field plus 24 secondary procedures) could have been recorded.

Both study samples only included the records of women who delivered during that particular hospitalization and were aged 14–45 years. The Florida dataset did not contain a unique patient identifier; however, the Texas dataset did contain such an identifier. This variable allowed the identification of patients who had repeated admissions. The majority (94·5%) of women had only one record in our overall Texas delivery file. If a woman had more than one record in the Texas delivery file then we included only one discharge record per patient in our analysis using both the unique identifier and the quarter of discharge variable. To clarify, the records were sorted by the unique identifier and the quarter of discharge and then the FIRST command in the SAS software package (SAS Institute Inc., USA) was used to retain the first record for women who had two or more discharges. However, we did not have the exact date of discharge and hence the sole record that was included for women who had repeated admissions within a particular calendar quarter (most likely due to antepartum complications) may not have been her first record from a chronological point of view. Deliveries in both databases were enumerated using ICD-9-CM diagnosis codes. If a patient had a code beginning

Table 1. *ICD-9-CM codes for the conditions under study*

| Condition | ICD-9-CM code(s) |
|---|---|
| **Exposure**: Maternal GBS colonization | V02.51 |
| **Outcome**: Pre-eclampsia/eclampsia | |
| Mild or unspecified pre-eclampsia | 642·40–642·44 |
| Severe pre-eclampsia | 642·50–642·54 |
| Eclampsia | 642·60–642·64 |
| Pre-eclampsia or eclampsia superimposed on pre-existing hypertension | 642·70–642·74 |
| **Potential confounders**: Maternal infections | |
| Bacteriuria (including asymptomatic bacteriuria, bacteriuria with urinary tract infection, and bacteriuria in pregnancy or puerperium) | 599·0, 646·50–646·54, 791·9 |
| Trichomoniasis (urogenital) | 131·00–131·02, 131·09 |
| Venereal disease due to *Chlamydia trachomatis* (lower genitourinary sites including vagina) | 099·53 |
| **Potential confounders**: Traditional risk factors* | |
| Cocaine dependence or abuse | 304·20–304·23, 305·60–305·63 |
| Diabetes (including gestational diabetes) | 250·00–250·93, 648·80–648·84 |
| Obesity (unspecified or morbid obesity) | 278·00, 278·01 |
| Primigravida† | 659·5, 659·8, V22.0, V23.81, V23.83 |
| Systemic lupus erythematosus | 710·0 |
| Tobacco dependence or history of tobacco use | 305·1, V15.82 |

ICD-9-CM, International Classification of Diseases, Ninth Revision – Clinical Modification; GBS, group B streptococcus.
* Other than demographic variables such as maternal age and race.
† See Methods section for detailed description and limitation.

with V27 in any of her diagnosis fields, then she was considered to have delivered during that hospital stay.

### Exposure and outcome definitions

The exposure (risk factor) of interest was maternal colonization with GBS. A woman was considered to be a GBS recto-vaginal carrier if her record had the ICD-9-CM code of V02.51 in any of her diagnosis fields. The V02 category is entitled, 'Carrier or suspected carrier of infectious diseases' and the V02.51 code specifically identifies the organism as GBS. The patient was assumed not be colonized with GBS if her electronic record lacked the V02.51 code.

The outcome was pre-eclampsia or eclampsia and was defined as the presence of any of the following ICD-9-CM codes in any of the diagnosis fields: 642·40, 642·41, 642·42, 642·43, 642·44, 642·50, 642·51, 642·52, 642·53, 642·54, 642·60, 642·61, 642·62, 642·63, 642·64, 642·70, 642·71, 642·72, 642·73, or 642·74.

### Statistical analysis

Cross-sectional prevalence studies were conducted where the binary outcome of interest was pre-eclampsia/eclampsia. Logistic regression was performed using the SAS System for Windows v. 9.1.3 (SAS Institute Inc., USA). Unadjusted and adjusted prevalence odds ratios (ORs) were calculated and reported with 95% confidence intervals (CIs) for the population ORs.

The GBS colonization OR was adjusted for maternal age (in years), race and Hispanic ethnicity, health insurance status, gravidity, and the maternal infections and comorbidities listed in Table 1. Socioeconomic status is correlated with the occurrence of many diseases. The health insurance variable was used as a surrogate measure of socioeconomic status. Our binary health insurance status variable was created using a multi-level variable found in the database that indicated the expected primary source of payment. Medicaid patients were compared to other patients. Medicaid is a programme originating from the federal government for individuals with limited resources such as low income.

Neither databases contained detailed information on the patient's gravidity and parity; however, several ICD-9-CM codes were used to attempt to identify a primigravida. These codes were 659·5 (elderly primigravida – a woman who will be $\geqslant$35 years at the expected date of delivery), 659·8 (young

https://doi.org/10.1017/S0950268812001598 Published online by Cambridge University Press

primigravida – a woman who will be $<16$ years at the expected date of delivery), V22.0 (supervision of a normal first pregnancy), V23.81 (supervision of a high-risk pregnancy, elderly primigravida – a woman who will be $\geqslant 35$ years at the expected date of delivery), and V23.83 (supervision of a high-risk pregnancy, young primigravida – a woman who will be $<16$ years at the expected date of delivery). ICD-9-CM codes for the supervision of high-risk pregnancies in women between the ages of 16 and 34 years do not exist.

It was possible that several of our independent variables were highly correlated (such as obesity and diabetes), a phenomenon known as collinearity. Collinearity can result in inaccurate estimates of regression coefficients and lead to reduced statistical power [8, 9]. A review of the tolerances revealed that collinearity was not present [10].

Initially 194 792 deliveries were identified in the Florida dataset. Of these deliveries 190 645 records met the inclusion criteria and had complete data on the dependent and independent variables. A total of 701 514 deliveries were identified in the Texas dataset. As described above, we used the unique patient identifier and the quarter of discharge variable to ensure that the dataset only included one record per patient. Applying this restriction led to a dataset with 580 318 records of which two had a missing value for the patient's sex and were deleted. The dataset of 580 316 records was considered the source population of subjects for the Texas analysis. After deleting records with missing values and restricting to those records which met our inclusion criteria, 577 153 records were available for study in the Texas dataset. This study was approved by the Institutional Review Board of the Texas Tech University Health Sciences Center School of Medicine at El Paso, El Paso, Texas.

## RESULTS

Tables 2 and 3 summarize the clinical and demographic characteristics of the Florida and Texas subjects, respectively. The overall prevalence of GBS carriage was 12·3% in the Florida sample (23 428 carriers/190 645 deliveries) (Table 2). The prevalence of the combined outcome of pre-eclampsia and eclampsia was lower in GBS carriers than in non-carriers.

The overall prevalence of GBS carriage was 14·1% (81 457 carriers/577 153 deliveries) while the overall prevalence of pre-eclampsia was 4·0% (22 998 cases/577 153 deliveries) in the Texas women (Table 3). About 46% of the women who were free of GBS were Medicaid beneficiaries.

ORs for pre-eclampsia/eclampsia are reported in Table 4. Each of the adjusted ORs (aORs) is adjusted for the remaining variables shown in Table 4. The aOR for the association between GBS carriage and outcome was 0·71 and was statistically significant in the Florida sample. A similar result was seen in the Texas patients: GBS carriers were 31% less likely than non-carriers to have a diagnosis of pre-eclampsia (aOR 0·69, 95% CI 0·66–0·72). In both states women in the youngest age group (14–19 years) and the oldest age group (40–45 years) were significantly more likely than women aged 20–29 years to have pre-eclampsia.

Bacteriuria, diabetes, obesity, and systemic lupus erythematosus were strongly correlated in a positive fashion with the prevalence of pre-eclampsia in both the hypothesis-generating (Florida) and the hypothesis-testing (Texas) databases (Table 4). Primigravidas were noted to have elevated odds of pre-eclampsia in both datasets. In regard to maternal race and ethnicity Black non-Hispanic patients were more likely than White non-Hispanic patients to have pre-eclampsia in Florida and Texas while patients in the Other race category were less likely to have pre-eclampsia compared to White non-Hispanics in both datasets (Table 4). Tobacco use or abuse reduced the odds of having pre-eclampsia in Texas women.

## DISCUSSION

In a group of women delivering throughout Texas in 2004 or 2005 we found that GBS carriage was inversely associated with pre-eclampsia (aOR 0·69). This result is similar to the aOR of 0·71 for the same association in the Florida hospital discharge database. The strengths of our study include its unique research question and large sample size. Even though we adjusted for well-known confounders, limitations of our study include the lack of data on partner change and birth interval [11, 12]. In addition, our control for the possible confounding effect of gravidity was not complete since there are no ICD-9-CM codes (non-V codes) identifying a primigravid woman who is aged between 16 and 34 years; as such, our primigravida variable did not capture the majority of women who were in their first pregnancy as evidenced by the low percentages reported in Tables 2 and 3. Linking our Texas dataset with a state government

Table 2. *Results from the hypothesis-generating dataset: clinical and demographic characteristics of 190 645 women who delivered in Florida and were discharged in 2001*

| Characteristic | GBS carrier ($N=23\,428$) Number (%) | GBS non-carrier ($N=167\,217$) Number (%) | $\chi^2$ *P* value |
|---|---|---|---|
| **Maternal age (years)*** | | | 0·02 |
| 14–19 | 2784 (11·9) | 20 339 (12·2) | |
| 20–29 | 12 090 (51·6) | 85 886 (51·4) | |
| 30–39 | 8021 (34·2) | 56 659 (33·9) | |
| 40–45 | 533 (2·3) | 4333 (2·6) | |
| **Race/ethnicity** | | | <0·0001 |
| White Hispanic | 3907 (16·7) | 34 877 (20·9) | |
| Black non-Hispanic | 5796 (24·7) | 35 456 (21·2) | |
| Other race/ethnicity | 1482 (6·3) | 10 206 (6·1) | |
| White non-Hispanic | 12 243 (52·3) | 86 678 (51·8) | |
| **Medicaid** | | | <0·0001 |
| Yes | 8494 (36·3) | 67 230 (40·2) | |
| No | 14 934 (63·7) | 99 987 (59·8) | |
| **Primigravida** | | | 0·20 |
| Yes | 459 (2·0) | 3074 (1·8) | |
| No | 22 969 (98·0) | 164 143 (98·2) | |
| **Comorbidities** | | | |
| Bacteriuria | 95 (0·4) | 1000 (0·6) | 0·0003 |
| Cocaine dependence or abuse | 47 (0·2) | 562 (0·3) | 0·0006 |
| Diabetes (including gestational diabetes) | 1155 (4·9) | 7470 (4·5) | 0·001 |
| Obesity (unspecified or morbid obesity) | 171 (0·7) | 1110 (0·7) | 0·25 |
| Systemic lupus erythematosus | 24 (0·1) | 113 (0·1) | 0·06 |
| Tobacco dependence or history of use | 476 (2·0) | 3930 (2·4) | 0·002 |
| Trichomoniasis | 4 (0·02) | 85 (0·1) | 0·03 |
| *Chlamydia trachomatis* venereal disease | 1 (0·0) | 8 (0·0) | 1† |
| **Outcome** | | | |
| Prevalence of pre-eclampsia/eclampsia | 651 (2·8) | 6400 (3·8) | <0·0001 |

GBS, Group B streptococcus.

* Median age of both GBS carriers and non-carriers was 27 years.

† Fisher's exact test.

vital statistics database would have given us access to information on parity and gravidity; however, our Texas data user agreement prohibits us from attempting data linkages.

We could not find any similar epidemiological studies of GBS colonization as a risk factor for pre-eclampsia. Our exploratory study also examined maternal infections. Rustveld and colleagues recently published the results of a meta-analysis of maternal infections and pre-eclampsia [5]. Their analysis included 16 studies and found that any maternal infection (bacterial or viral) doubled the odds of pre-eclampsia (OR 2·1, 95% CI 1·6–2·7). Conde-Agudelo *et al.* also recently conducted a meta-analysis of the same research question [13]. They reported that women with a urinary tract infection were more likely to develop pre-eclampsia than women without a urinary tract infection (pooled OR 1·57, 95% CI 1·45–1·70). We detected significantly elevated odds for pre-eclampsia associated with bacteriuria (including bacteriuria with urinary tract infection) in both datasets (aOR 2·42 in the Texas sample) (Table 4).

Whether or not GBS status influences the risk of pre-eclampsia can be evaluated with traditional causality criteria which include the strength of the association, consistency with other investigations, and biological credibility/plausibility [14, 15]. In regard to the latter causal criterion, a possible inverse relationship between GBS colonization and the risk of pre-eclampsia is biologically plausible and probably involves cytokines such as tumor necrosis factor (TNF)-$\alpha$ and interleukin-6 (IL-6). GBS induces production of TNF-$\alpha$ [16–19] and IL-6 [17–19]. TNF-$\alpha$ is

https://doi.org/10.1017/S0950268812001598 Published online by Cambridge University Press

Table 3. *Results from the hypothesis-testing dataset: clinical and demographic characteristics of 577 153 women who delivered in Texas and were discharged in 2004 or 2005*

| Characteristic | GBS carrier ($N=81\,457$) Number (%) | GBS non-carrier ($N=495\,696$) Number (%) | $\chi^2$ $P$ value |
|---|---|---|---|
| **Maternal age (years)*** | | | <0·0001 |
| 14–19 | 10 202 (12·5) | 68 325 (13·8) | |
| 20–29 | 43 730 (53·7) | 265 045 (53·5) | |
| 30–39 | 25 934 (31·8) | 151 539 (30·6) | |
| 40–45 | 1591 (2·0) | 10 787 (2·2) | |
| **Race/ethnicity** | | | <0·0001 |
| White Hispanic | 8209 (10·1) | 74 678 (15·1) | |
| Black non-Hispanic | 12 628 (15·5) | 54 599 (11·0) | |
| Other race/ethnicity | 25 502 (31·3) | 174 909 (35·3) | |
| White non-Hispanic | 35 118 (43·1) | 191 510 (38·6) | |
| **Medicaid** | | | <0·0001 |
| Yes | 32 194 (39·5) | 226 922 (45·8) | |
| No | 49 263 (60·5) | 268 774 (54·2) | |
| **Primigravida** | | | <0·0001 |
| Yes | 1664 (2·0) | 11 800 (2·4) | |
| No | 79 793 (98·0) | 483 896 (97·6) | |
| **Comorbidities** | | | |
| Bacteriuria | 378 (0·46) | 2804 (0·57) | 0·0003 |
| Cocaine dependence or abuse | 62 (0·08) | 1191 (0·24) | <0·0001 |
| Diabetes (including gestational diabetes) | 3988 (4·9) | 24 387 (4·9) | 0·77 |
| Obesity (unspecified or morbid obesity) | 788 (0·97) | 4187 (0·84) | 0·0004 |
| Systemic lupus erythematosus | 57 (0·07) | 362 (0·07) | 0·76 |
| Tobacco dependence or history of use | 1444 (1·8) | 8103 (1·6) | 0·004 |
| Trichomoniasis | 20 (0·02) | 122 (0·02) | 0·99 |
| *Chlamydia trachomatis* venereal disease | 8 (0·01) | 34 (0·01) | 0·36 |
| **Outcome** | | | |
| Prevalence of pre-eclampsia/eclampsia | 2372 (2·9) | 20 626 (4·2) | <0·0001 |

GBS, Group B streptococcus.
* Median age of both GBS carriers and non-carriers was 26 years.

associated with and may be a causal factor in pre-eclampsia [20–25]. IL-6 may play a similar role [26, 27]. TNF-$\alpha$ is capable of desensitizing its receptors so that the signal from its receptors is diminished upon repeated stimulation [28–30]. In addition, TNF exposure may decrease IL-6 expression [31]. A possible explanation for the decreased prevalence of pre-eclampsia in our population is that the TNF-$\alpha$ receptors in GBS-colonized women are relatively desensitized by long-term prior exposure to TNF-$\alpha$.

We report an aOR for the association between GBS (carriers *vs.* non-carriers) and the outcome of pre-eclampsia of 0·69 in Texas patients. The reciprocal of this OR (1·45) indicates that GBS-negative women were 45% more likely than GBS-positive women to have pre-eclampsia. It may be argued that this result is due to reverse causality bias: GBS-negative status does not lead to pre-eclampsia, but rather pre-eclampsia leads to an early delivery, a delivery before the traditional GBS screening period of 34–36 weeks [32], and therefore a proportion of GBS-positive women may have been misclassified as GBS-negative in our study. However, this argument is specious given the results of a recent large cohort study of singleton births which found that the majority (84%) of women who developed pre-eclampsia during their first pregnancy delivered at 37 weeks or beyond [12]. Furthermore, if the results of GBS recto-vaginal cultures are not available upon admission with the diagnosis of pre-eclampsia, then the obstetrician typically orders a rapid GBS test (a polymerase chain reaction test) before delivering the patient.

The exact gestational age at the time of delivery was not recorded on the maternal record in our database; however, using ICD-9-CM codes for premature

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Table 4. *Results from the hypothesis-generating dataset* (*Florida*) *and the hypothesis-testing dataset* (*Texas*)*: adjusted prevalence odds ratios for pre-eclampsia/eclampsia*

| | Florida ($N=190\,645$) | | Texas ($N=577\,153$) | |
|---|---|---|---|---|
| Potential risk factor | aOR* | 95% CI | aOR* | 95% CI |
| GBS carrier (yes *vs.* no) | 0·71 | 0·65–0·77 | 0·69 | 0·66–0·72 |
| **Demographic and epidemiological variables** | | | | |
| Age (years) | | | | |
| 14–19 | 1·45 | 1·36–1·56 | 1·47 | 1·42–1·53 |
| 20–29 | 1 | Referent | 1 | Referent |
| 30–39 | 1·01 | 0·95–1·07 | 0·97 | 0·94–1·00 |
| 40–45 | 1·33 | 1·16–1·53 | 1·39 | 1·29–1·51 |
| Race/ethnicity | | | | |
| White Hispanic | 1·01 | 0·94–1·08 | 1·32 | 1·27–1·37 |
| Black non-Hispanic | 1·55 | 1·47–1·65 | 1·37 | 1·32–1·43 |
| Other race/ethnicity | 0·79 | 0·70–0·89 | 0·90 | 0·87–0·93 |
| White non-Hispanic | 1 | Referent | 1 | Referent |
| Medicaid health insurance (yes *vs.* no) | 1·10 | 1·04–1·16 | 1·00 | 0·97–1·03 |
| Primigravida (yes *vs.* no) | 1·66 | 1·45–1·91 | 1·26 | 1·16–1·36 |
| **Comorbidities (present *vs.* absent)** | | | | |
| Bacteriuria | 2·24 | 1·81–2·78 | 2·42 | 2·15–2·72 |
| Cocaine use | 1·18 | 0·81–1·73 | 1·13 | 0·86–1·47 |
| Diabetes | 2·02 | 1·85–2·21 | 2·14 | 2·04–2·24 |
| Obesity | 4·07 | 3·47–4·76 | 3·38 | 3·11–3·68 |
| Systemic lupus erythematosus | 3·11 | 1·78–5·43 | 2·62 | 1·89–3·63 |
| Tobacco use | 0·86 | 0·72–1·02 | 0·87 | 0·78–0·97 |
| Trichomoniasis | 2·86 | 1·54–5·30 | 1·38 | 0·72–2·63 |
| *Chlamydia trachomatis* | –† | –† | 0·51 | 0·07–3·70 |

aOR, Adjusted odds ratio; CI, confidence interval; GBS, group B streptococcus.
* Each odds ratio is adjusted for the remaining variables in the table.
† Could not be calculated due to a very small number ($n=9$) of patients with this infection.

labour with onset of delivery before 37 completed weeks of gestation we were able to calculate stratum-specific GBS ORs. Overall, 7·4% of the sample experienced preterm labour (data not shown) and the GBS OR for pre-eclampsia in women who had experienced preterm labur (aOR 0·67, 95% CI 0·59–0·75) and the GBS OR in the larger group of women who did not experience preterm labour (aOR 0·77, 95% CI 0·74–0·81) support the assertion that GBS-positive women have at least a 23% reduction in the odds of having pre-eclampsia (0·77 minus the null value of 1).

Similarly, it may be argued that pre-eclampsia inevitably leads to a caesarean delivery thereby precluding the need for a vaginal culture [32] which would lead to an unknown GBS status and the erroneous classification of these women as GBS-negative in our dataset. However, pre-eclampsia by itself is not an indication for caesarean delivery. Obstetricians and maternal-fetal medicine specialists prefer to deliver pre-eclamptic women vaginally as this is associated with lower maternal morbidity.

Several factors influence a pre-eclamptic woman's risk of caesarean delivery, but the majority of pre-eclamptic women undergo vaginal delivery. A study using Missouri birth certificate data found that women with pre-eclampsia treated at tertiary-care hospitals were less likely than women treated at primary and secondary hospitals to undergo a caesarean delivery [33]. The caesarean delivery rates in the Missouri study were 30% in women treated at tertiary-care facilities *vs.* 38·0% and 33·7% for women treated at primary and secondary hospitals, respectively. The authors concluded, 'Levels of expertise and staffing at tertiary hospitals may allow greater attempts and success with vaginal delivery among women with pre-eclampsia compared with primary or secondary hospitals' [33]. In our analysis of Texas data, 33·8% of the 577153 women ($n=194\,958$) underwent a caesarean delivery, and the GBS aOR for pre-eclampsia in this group of women

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Table 5. *Results of a sensitivity analysis of misclassification of group B streptococcus (GBS) carrier status in 577 153 women who delivered in Texas and were discharged in 2004 or 2005. GBS carrier status was the exposure variable while pre-eclampsia/eclampsia was the outcome*

| Women who developed pre-eclampsia | | Women who did not develop pre-eclampsia | | Type of misclassification of GBS status† | Corrected odds ratio comparing GBS carriers with non-carriers |
|---|---|---|---|---|---|
| Sensitivity* | Specificity* | Sensitivity* | Specificity* | | |
| 85 % | 93 % | 85 % | 93 % | Non-differential | 0·43 |
| 85 % | 95 % | 85 % | 95 % | Non-differential | 0·54 |
| 91 % | 91 % | 91 % | 91 % | Non-differential | 0·24 |
| 80 % | 95 % | 90 % | 95 % | Differential | 0·62 |
| 90 % | 95 % | 90 % | 90 % | Differential | 1·18 |
| 94 % | 91 % | 85 % | 91 % | Differential | 0·21 |

* Sensitivity and specificity of the measurement of GBS status.

† Non-differential or random misclassification is present if pre-eclamptic women were just as likely as women free of pre-eclampsia to have their GBS status misclassified. Differential or non-random misclassification indicates that the pre-eclamptic cases were more likely or less likely than non-cases to have their GBS status misclassified.

was 0·68 (95 % CI 0·64–0·73) while the GBS aOR for pre-eclampsia in the larger group of women who did not undergo a caesarean delivery was attenuated (closer to the null value of 1) but still statistically significant (aOR 0·81, 95 % CI 0·77–0·86).

A limitation of our study is that a proportion of our sample was no doubt treated empirically for GBS colonization. This figure is impossible to determine without reviewing the medical records. To clarify, if, for whatever reason, the result of a GBS culture or GBS rapid test was not available yet the delivery was imminent then most woman would be administered intrapartum antibiotics to prevent the vertical transmission of GBS. For the purposes of statistical analyses, these women should be classified as having an 'unknown' or 'missing' value for GBS status. Since our study was not prospective these women with an unknown GBS status were classified as being GBS-negative. The results of a sensitivity analysis using standard formulae [34] revealed that even in the presence of misclassification of the exposure variable (GBS status) the majority of the corrected ORs are $<1$ indicating a protective effect of GBS colonization (Table 5). Nonetheless, future studies should attempt to validate the ICD-9-CM code for GBS carrier status by comparing hospital discharge data with medical records and calculating the sensitivity and the specificity.

Several recent investigations have used the Texas and Florida hospital inpatient discharge databases to explore the epidemiology of pre-eclampsia [35–38]. Misclassification of the presence of pre-eclampsia in these previous studies and in the current investigation is possible. While there are no published reports on the accuracy of the coding of pre-eclampsia in Texas or Florida inpatient datasets, a study conducted by Yasmeen *et al.* found that the ICD-9-CM coding of pre-eclampsia (any type) in California hospital discharge data was accurate: sensitivity 88 %, positive predictive value 91 % [39].

The causal pathways of pre-eclampsia are complex and hence a large prospective study is needed to elucidate its multiple risk factors and modifiers. Such a study will allow the calculation of the proportion of pre-eclampsia in GBS carriers that is attributable to their GBS colonization. This statistic, the attributable risk percent, should also be estimated for various maternal genitourinary tract infections. In conclusion, our cross-sectional analyses of two large statewide databases found that women who were GBS carriers had lower odds of pre-eclampsia than non-carriers. We envision that our results, which are exploratory in nature, will stimulate both epidemiological and laboratory studies that may elucidate portions of the complicated causal pathways of pre-eclampsia thereby revealing opportunities to prevent this serious pregnancy-specific syndrome. Further investigation of this research question using cohort studies is warranted.

## ACKNOWLEDGEMENTS

The authors acknowledge the use of the Texas Hospital Inpatient Discharge Public Use (and Research Use) Data File, quarters 1–4 for years 2004 and 2005, Texas Department of State Health Services,

Center for Health Statistics–Texas Health Care Information Collection (THCIC), Austin, Texas, USA.

## DECLARATION OF INTEREST

The leasing of these data was supported in part by a grant from the Laura W. Bush Institute for Women's Health at the Texas Tech University Health Sciences Center in Amarillo, Texas, USA. The Institute did not guide our research or have any other role other than that of funder.

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