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Major article

Diabetes and early postpartum methicillin-resistant *Staphylococcus aureus* infection in US hospitals

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Background: The epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in postpartum women is not well characterized. Because diabetes is a risk factor for some infections, we sought to characterize the relationship between diabetes and invasive MRSA infections in women admitted to US hospitals for delivery of an infant.

Methods: We used data from the Nationwide Inpatient Sample, a representative sample of US community hospitals. Multivariate hierarchical logistic regression was used to estimate odds ratios (OR), adjusting for age, race, selected comorbidities, and expected payer, and hospital teaching status, urbanicity, bed size, geographic region, and ownership.

Results: The odds ratio for prepregnancy diabetes was 3.4 (95% confidence interval: 1.9-6.0). The relationship remained strong after external adjustment for obesity (OR, 2.5; 95% CI: 1.3-4.8). The OR comparing women with complicated versus uncomplicated diabetes was 1.5 (95% CI: 0.3-6.0). We did not find an association with gestational diabetes (OR, 1.1; 95% CI: 0.7-1.7).

Conclusion: Prepregnancy diabetes, but not gestational diabetes, appears to be a risk factor for invasive MRSA infection in the early postpartum period. Women with diabetic complications may be at additional risk, but estimates were imprecise.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to *S aureus* strains that have developed resistance to β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems.[1] Compared with patients uninfected with *S aureus* or infected with methicillin-susceptible *S aureus*, MRSA-infected patients have longer hospital stays, greater mortality, and higher charges.[2-5]

There are few published reports on the epidemiology of invasive MRSA infections among postpartum women at the national level. In 2009, Beigi et al used decision analysis modeling to estimate that MRSA causes 5,414 cases of surgical wound infections and 8,800 cases of mastitis in postpartum women but noted that they were unable to find any empirical data on the burden of invasive MRSA infections in pregnant or postpartum women.[6] Using data from the Nationwide Inpatient Sample, we previously estimated that there were approximately 2,600 cases of invasive MRSA infection diagnosed each year in obstetric inpatients.[7]

A number of case reports and case series discuss cases of MRSA infections in postpartum women. Mastitis, cellulitis, breast abscess, pelvic thrombophlebitis, pneumonia, septicemia, wound infection (cesarean and episiotomy), and urinary tract infections have been reported.[6,8-11] Three case control studies and 1 cohort study with a nested case control component examined predictors of postpartum MRSA infections in 5 different medical centers.[10,12-14] Two longitudinal studies found increasing rates of MRSA infections over time.[12,14] *S aureus* breast abscesses, including those caused by MRSA, were associated with maternal employment outside the home and breastfeeding difficulties.[14]

The aims of this study are to investigate (1) the extent to which prepregnancy and gestational diabetes are associated with MRSA infection among women hospitalized for delivery in the United States; and (2) whether, among women with prepregnancy diabetes, diabetic complications were associated with MRSA infection. Persons with diabetes mellitus are known to be at increased risk for certain types of infections, including urinary tract infections, surgical wound infections, and other skin and soft-tissue infections. Outside of obstetric settings, persons with diabetes are at increased risk of MRSA infection and may also be more likely to be

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asymptomatic carriers of *S aureus*.[1,15] Diabetes also appears to be a risk factor for cesarean section, which in turn is a risk factor for postpartum infection.[16-19]

METHODS

Data source

For this study, we used data from the Nationwide Inpatient Sample (NIS). The NIS is a stratified probability sample of approximately 20% of US community hospitals, defined by the American Hospital Association as "all non-federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions." Seven states (Alabama, Alaska, Idaho, Mississippi, Montana, New Mexico, and North Dakota) do not provide data to the NIS, and some states do not report data from all hospitals. However, the NIS sampling strategy is designed to create a sample that is representative of all US community hospitals, including those excluded from the sampling frame.[20] The NIS is a part of the Healthcare Cost and Utilizations Project, a federal, state, and industry partnership funded by the Agency for Healthcare Research and Quality.

Among hospitals included in the NIS, all inpatient discharges are reported. The NIS contains both hospital and patient level data. For patient level data, there is one record for each inpatient admission. Thus, one individual may contribute to multiple observations.

The study group consisted of women in the NIS from 2005 through 2008 who were admitted for delivery (defined by Diagnosis Related Groups 370-375). Because the NIS is a public use database, this study was exempt from review by the Institutional Review Board of the University of California, Los Angeles.

Outcome definition

The outcome of interest was invasive MRSA infection prior to discharge after hospitalization for the delivery of an infant. In 2008, several new ICD-9 CM codes indicating MRSA infection or carriage were introduced including 038.12 (MRSA septicemia), 482.42 (methicillin-resistant pneumonia due to *S aureus*), and 041.12 (MRSA in conditions classified elsewhere and of unknown site), which were used to define invasive MRSA infections in 2008 admissions. Prior to 2008, invasive MRSA infection was defined by presence of ICD-9 codes 482.41 (*S aureus* pneumonia), 038.11 (*S aureus* septicemia), or 041.11 (MRSA in conditions classified elsewhere and of unknown site) along with code V09.0 (infection with microorganisms resistant to penicillins). This definition of MRSA infection has been used by the Healthcare Cost and Utilization project.[2]

Exposure definition

Elixhauser comorbidity measures for uncomplicated diabetes and diabetes with complications are included in the NIS. The Elixhauser comorbidity measures are dichotomous variables derived from hospital administrative data, which seek to characterize the presence of chronic illnesses that are unrelated to the principal diagnosis but may impact mortality, morbidity, hospital charges, or length of stay.[21]

There are 2 Elixhauser comorbidity measures for prepregnancy diabetes mellitus: uncomplicated diabetes and diabetes with chronic complications.[21] These 2 variables were recoded using nested indicator models. One variable was created for the presence of diabetes mellitus and is equal to 1 for all women with either complicated or uncomplicated diabetes and equal to zero for all other women. A second variable was created for diabetic complications and is equal to 1 for diabetes with complications and equal to zero for both women with uncomplicated diabetes and women without diabetes. This coding allowed association measures for the second variable to be interpreted as comparing women with complicated diabetes to those with uncomplicated diabetes, rather than women without diabetes.[22]

Gestational diabetes was defined using ICD-9 CM codes 648.80 through 648.84. It was coded as a dichotomous variable with a value of 1 for women with gestational diabetes and zero for those without.

Six hundred eleven women had diagnoses of both gestational diabetes and prepregnancy diabetes. Nineteen of these also had a diagnosis of diabetic complications. Because gestational diabetes refers to diabetes with onset or first diagnosis in pregnancy,[23] prepregnancy diabetes and gestational diabetes are mutually exclusive diagnoses, and these women can be considered to be misclassified with respect to prepregnancy diabetes status, gestational diabetes status, or both. For the primary analysis, we excluded these 611 women. For comparison, we also ran 3 separate models where the 611 "dual-diagnosis" women were classified as (a) prepregnancy diabetics, (b) gestational diabetics, and (c) a separate exposure category.

Potential confounders

Age and race are both predictors of both diabetes and MRSA infection and thus should be considered potential confounders.[2,24-26] Race is included in the NIS as a 6 level variable with possible values of white, black, Hispanic, Asian or Pacific Islander, Native American, or "other." Because of the small number of Native American women in the sample, for the purposes of this analysis, they are included in the "other" category.

Diabetes is also more prevalent among persons of lower socioeconomic status.[27,28] Although we found no studies that examined risk of MRSA by socioeconomic status, persons of low socioeconomic status are at increased risk of many diseases, including a number of infectious diseases.[29,30] Expected payer (of medical expenses) is used as a proxy for socioeconomic status. Categories used are private insurance, Medicaid, and other payers (a collapsed category that includes Medicare, self pay, no charge, and other payers).

Comorbidities may confound the association between diabetes and MRSA infection. HIV infection is immunosuppressive, and HIV-infected persons are more susceptible to MRSA infection.[1] Impaired glucose tolerance and increased susceptibility to diabetes mellitus are known to be adverse effects of anti-HIV medications.[31] Other comorbidities may increase risk of MRSA infection by increasing contact with medical care facilities and personnel. Hypothyroidism can be a result of autoimmunity and appears to share common causes with type 1, and to a lesser extent, type 2 diabetes.[32,33] Psychosis was also included in the analysis because antipsychotic medications appear to predispose users to insulin resistance and diabetes.[34] Liver disease is known to cause diabetes, likely because of defects in glycogen synthesis.[35] Elixhauser comorbidity codes for liver disease, HIV infection, hypothyroidism, and psychosis are included in the NIS.

Data analysis

Multivariate associations were analyzed using hierarchical logistic regression with random intercepts. Patients' admissions were nested within hospitals. In addition to the potential confounders listed above, variables used in construction of the sampling frame were included in the analysis. These include geographic region (Southeast, Northeast, Midwest, or West) and hospital bed size, teaching status, urbanicity, and ownership.

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