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Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease

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Abstract

Purpose—Systemic sclerosis (SSc), primary pulmonary hypertension (PPH), and sickle cell disease (SCD) are uncommon vasculopathic diseases affecting women. We estimated the nationwide occurrence of pregnancies in women with these conditions and compared pregnancy outcomes to the general obstetric population.

Methods—We studied the 2002–2004 Nationwide Inpatient Sample (NIS), of the Healthcare Cost and Utilization Project to estimate the number of obstetric hospitalizations and deliveries among women with SSc, PPH, SCD, and the general population. Pregnancy outcomes included length of hospital stay (LOS), hypertensive disorders including preeclampsia (HTN), intrauterine growth restriction (IUGR), and cesarean delivery. Multivariable regression analyses were performed using maternal age, race/ethnicity, antiphospholipid antibody syndrome, diabetes mellitus, and renal failure as covariates.

Results—Of an estimated 11.2 million deliveries, 504 occurred in women with SSc, 182 with PPH, and 4,352 with SCD. SSc was associated with an increased risk of HTN (OR 3.71, 95%CI 2.25–6.15), IUGR (OR 3.74, 95%CI 1.51–9.28), and increased LOS. PPH was associated with an increase in the odds of antenatal hospitalization (OR 4.67, 95%CI 2.88–7.57), HTN (OR 5.62, 95%CI 2.60–12.15) and a substantial increase in LOS. SCD was associated with an increased odds of antenatal hospitalization (OR 5.55, 95%CI 5.08–6.09), HTN (OR 1.78, 95%CI 1.48–2.14), and IUGR (OR 2.91, 95%CI 2.16–3.93), with a modest increase in LOS.

Conclusions—Women with SSc, PPH, and SCD have significantly increased rates of adverse pregnancy outcomes, requiring extensive preconceptional counseling about the risks of pregnancy. All pregnancies should be monitored closely for the development of complications.

Keywords

Pregnancy; sickle cell disease; systemic sclerosis; pulmonary hypertension; outcomes; hospitalization

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Conflicts of Interest: None

Introduction

Systemic sclerosis (SSc), primary pulmonary hypertension (PPH) and sickle cell disease (SCD) are chronic diseases that are associated with non-inflammatory vasculopathy and can be associated with significant morbidity and mortality [1–4]. In the past, pregnancy was contraindicated in these patients due to a high incidence of maternal and fetal death [5–7]. With improvements in diagnosis, follow-up and treatment of these diseases and with careful and enhanced prenatal care in the past several years, increasing numbers of women are proceeding with pregnancy. Recent reports have demonstrated more favorable pregnancy outcomes in women with these diseases [8,9]. Because these diseases are relatively rare, published studies of pregnancy outcomes have been limited by small numbers of patients and long periods of observation during which temporal trends in medical therapy had changed significantly. Most past studies were retrospective, performed at single, tertiary-care centers, and may not accurately reflect pregnancy outcomes throughout the United States. We utilized a large inpatient care database which is representative of care provided in US community hospitals to assess 1) obstetric hospitalizations and deliveries and 2) pregnancy outcomes and their predictors in patients with SSc, PPH, and SCD.

Materials and Methods

We utilized the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project [10] for the years 2002–2004. The NIS, established in 1988, is the largest all-payer inpatient care database that is publicly available in the United States and contains clinical and demographic information available from discharge abstracts. The database contains information from all inpatient hospitalizations in 995 hospitals, which were sampled to approximate a 20% stratified sample of community hospitals in the US. The 2002 sample was drawn from hospitals in 35 states: California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, Nevada, New Jersey, New York, North Carolina, Ohio, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, and Wisconsin. In addition, the 2003 sample included Indiana and New Hampshire; and the 2004 database included Arkansas. The NIS includes all the non-federal short-stay hospitals listed by the American Hospital Association. These hospitals were divided into 60 strata based on region, location, teaching status, bed size category, and ownership. Within each stratum, a systematic random sample of hospitals was drawn, equal in size to 20% of that stratum. Detailed information on the design of the survey and the magnitude of sampling errors associated with the estimates is available in the technical documentation [11].

Information available from discharge abstracts included maternal age, length of hospital stay (LOS), principal diagnosis, up to 14 secondary diagnoses, principle procedure, and up to 14 secondary procedures. Data on race and ethnicity were collected in all but 11 states: categories included white, black, Hispanic, Asian and Pacific Islander, Native American, and other. We collapsed Native Americans into other due to few numbers of observations. Diagnoses and procedures were coded by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) codes [12]. Because unique patient identifiers were not provided to protect individual privacy in this publicly available data set, we used hospitalization, rather than patient, as the unit of analysis. Additionally, the lack of unique patient identifiers precluded linking of maternal to infant discharge records, thus, data on neonatal outcomes were not available.

All obstetric hospitalizations were included in the analysis. Hospitalizations were ascribed to the diagnosis (SSc [ICD-9-CM 710.1], PPH [416.0], and SCD [includes HB-SS, HB-SC,

HB-SD, and HB-SE disease, ICD-9-CM 282.60-282.69]) found among discharge diagnoses. Patients with sickle cell trait were excluded from all analyses. The control group was defined as any obstetric hospitalization in women who did not have a diagnosis of SSc, PPH, or SCD. Hospitalizations that were associated with delivery of an infant were defined as any hospitalization with procedure codes for cesarean section and other procedures for inducing or assisting delivery, or ICD-9-CM codes for normal delivery and delivery with complications. All other hospitalizations were considered antenatal hospitalizations that did not result in delivery. Comorbid conditions of interest included diabetes mellitus, antiphospholipid antibody syndrome, and renal failure.

Because SSc and PPH are rare diseases and pregnancy is uncommon among these patients, we combined data from three years for all 3 diseases of interest to ascertain enough cases amenable for analysis. Hospital and discharge weights were applied to the sample data to estimate the total number of obstetric hospitalizations, delivery-associated hospitalizations, and cesarean delivery for women with SSc, PPH, SCD, and the general obstetric population for the years 2002–2004. National estimates and 95% confidence intervals (95% CI) were calculated.

For each group of patients (SSc, PPH, SCD, and control), the maternal age and LOS were calculated, and differences in means were compared using analysis of variance (ANOVA) with the Dunnett's test for multiple comparisons to a control group. The proportion of hospitalizations for each group with the following pregnancy outcomes was calculated: antenatal hospitalizations, hypertensive disorders including preeclampsia (HTN), premature rupture of membranes (PROM), cesarean section, and intrauterine growth restriction (IUGR). As for diagnosis of underlying vasculopathic disease, all obstetric outcomes were obtained using ICD-9 codes. Hypertensive disorders of pregnancy include blood pressure greater than 140/90 and fall into the following categories: gestational hypertension, preeclampsia, eclampsia, and superimposed preeclampsia[13]; PROM is generally defined as rupture of amniotic sac prior to the onset of labor [14]; and IUGR is defined as weight <10 percentile of gestational age [15]. Chi-square and Fisher's exact tests were applied as appropriate to compare differences in rates between each group and the control population.

For each dichotomous outcome of interest (antenatal hospitalization, HTN, IUGR, and cesarean delivery), logistic regression was performed for each disease using maternal age as a covariate. For LOS (in days), linear regression was performed. Multivariable analyses were then performed for each outcome using maternal age, race/ethnicity and other clinically important variables including the antiphospholipid antibody syndrome, diabetes mellitus, and renal failure. Missing values were considered missing at random. Except for antenatal hospitalizations, all analyses were performed on the subset of hospitalizations that resulted in delivery of an infant in order to eliminate bias from multiple hospitalizations of sicker patients.

All analyses were performed using STATA Version 8.0 software (Stata, College Station, TX). An institutional review board waiver was obtained to use this publicly available, deidentified data.

Results

Obstetric hospitalizations

There were 2,893,904 obstetric hospitalizations in the NIS database between 2002 and 2004. Of these, 149 occurred in women with a discharge diagnosis of SSc, 85 in women with PPH, and 2,478 in women with SCD. One hospitalization carried diagnoses of both SSc and PPH and four with both SSc and SCD: these pregnancies were excluded from further analysis.

After application of sampling weights, there were an estimated 14 million total obstetric hospitalizations over the three years of study: approximately 695 in women with SSc, 407 in women with PPH, and 11,928 in women with SCD (Table 1). Of these hospitalizations, we estimated approximately 11.2 million total deliveries (95% CI 10.6–11.8 million) over the three years: 3.72 (3.36–4.07) million in 2002, 3.66 (3.31–4.01) million in 2003, and 3.83 (3.46–4.20) million in 2004. Estimates for deliveries by diagnosis group were 504 in women with SSc, 182 with PPH, and 4,352 with SCD. The distribution of patients among hospitals with small, medium, and large bed sizes was similar among all groups. Thirty-one to 40% of patients with SSc, PPH, and SCD were admitted to non-teaching hospitals (data not shown).

Demographic of patients

The mean age for all obstetric hospitalizations is 27.5 years (SD 6.2), and mean age for women delivering an infant was 27.5 (SD 6.2) years (Table 2). Women with SSc were an average of 2.0 (95% CI 0.7–3.3, $p<0.05$) years older and women with PPH were an average of 4.3 (95% CI 2.6–6.0, $p<0.05$) years older than controls. In contrast, women with SCD were an average of 2.9 (95% CI 2.6–3.2, $p<0.05$) years younger than controls.

Only 11 participating states did not report data on race/ethnicity. The distribution of race/ethnicity among patients with SSc did not differ appreciably from the general obstetric population (Table 2). Among PPH patients, the distribution of race and ethnicity was similar between white, black and Hispanic. This result is in contrast to reports of the distribution by race of patients with PPH in a national registry, where only a minority of patients were black (12.3%) or Hispanic (2.3%) [16]. As was expected, patients with SCD were almost exclusively black, with a low proportion of patients of other ethnicities.

Pregnancy outcomes

The proportion of obstetric admissions that were not associated with delivery (antenatal hospitalizations) in the control group was 19.6%. In comparison, 26.3% of SSc admissions were for complications of pregnancy not associated with delivery ($p=0.03$ compared to controls); and greater than half of admissions for patients with PPH (55.3%) and SCD (63.4%) did not result in the delivery of an infant ($p<0.001$). Additional pregnancy outcomes for hospitalizations associated with delivery by diagnosis group are shown in Table 3.

Women in all three disease groups had significantly increased LOS and rates of HTN that were two to four-fold higher than the control population. Rates of IUGR were significantly higher in women with SSc and SCD, but not with PPH. Cesarean deliveries were frequent in all groups (42.2% in SSc, 57.9% in PPH, 44.5% in SCD, and 31.1% in controls; $p<0.05$ vs. controls). There were too few events to compare rates of maternal death or fetal demise in this dataset.

Risk of adverse obstetric outcomes

Results of multivariable analyses examining the risk of adverse outcomes in obstetric hospitalizations are shown in Table 4. Except for antenatal hospitalizations, all analyses were performed on the subset of hospitalizations associated with delivery. SSc was independently associated with an increased risk of HTN (OR 3.71, 95% CI 2.25–6.15), IUGR (OR 3.74, 1.51–9.28), and increased LOS (β 2.50, 95% CI 2.07–2.95). A diagnosis of PPH was associated with a 5-fold increase in the odds of an antenatal hospitalization and hypertensive disorders of pregnancy. Similarly, PPH was associated with a markedly prolonged LOS. An elevated odds of IUGR was noted, but the 95% confidence intervals were wide and crossed the null. A diagnosis of SCD was associated with increased odds of antenatal hospitalization, HTN and IUGR, with a modest increase in the LOS.

As demonstrated in other studies of perinatal outcomes, black race was associated with slightly, but statistically significant, elevated odds of all adverse outcomes of interest, independent of the disease group [17,18]. In contrast, parturients of Hispanic or Asian ethnicity had lower rates of all adverse outcomes irrespective of diagnosis, with the exception of IUGR among Asian women [17–19].

Discussion

SSc, PPH, SCD are all vasculopathic disorders that can occur in women during the childbearing years. In past decades, women were strongly advised to avoid pregnancy because of poor perinatal outcomes for both mother and infant [5–7]. More recently, pregnancies have become slightly more common among women with these underlying diseases [5,20,21]. Despite this, studies have been limited by small numbers of patients collected at tertiary care medical centers, and changes in perinatal care over long periods of accrual. Using data available from the NIS from the years 2002–2004, we compared pregnancy outcomes among women with SSc, PPH, and SCD to those in the general obstetric population. The numbers of live births in the control group for each year is similar to those reported by vital statistics for each year and is encompassed within our confidence intervals [22–24]. We estimated nearly 4,400 deliveries among women with SCD during the three years of observation, compared with a much smaller number of approximately 504 deliveries in women with SSc and 182 in women with PPH. In addition, we found women with SSc and PPH were significantly older than the control group. This result is consistent with an older age of diagnosis of these diseases in addition to the possibility that women diagnosed with these diseases may delay pregnancy because of medication use or other disease-related factors. We found significantly increased rates of antenatal hospitalization, hypertensive disorders of pregnancy, IUGR, and cesarean delivery among women with SSc, PPH, and SCD compared with the general obstetric population. The increased risk of developing these pregnancy complications persisted after adjustment for maternal age, race/ethnicity, and co-morbid conditions including diabetes mellitus, renal failure, and the antiphospholipid antibody syndrome.

SSc is a rare female-predominant autoimmune disease of unclear etiology that is characterized by progressive fibrosis of the skin and internal organs and a non-inflammatory vasculopathy [25,26]. The mean age of onset is in the fifth decade, and 10-year survival has improved from 54% in the 1970s to 66% in the later 1990s [25,26]. Previous studies of pregnancy outcomes in women with SSc at single tertiary care centers have shown an increased frequency of preterm births and small for gestational age infants [9,27,28]. Likewise, our study showed a 3.7-fold increased risk of IUGR in SSc-associated pregnancies compared with controls. These findings could be explained by the underlying vasculopathy associated with SSc leading to placental insufficiency and infarction [29,30]. Earlier studies did not find high rates of hypertensive disorders of pregnancy in patients with SSc [9,27,28]. In contrast, our study found a nearly four-fold increased risk for HTN in SSc-associated pregnancies compared with controls. It is possible that SSc patients treated at tertiary care centers had more vigilant surveillance and treatment of HTN than at community hospitals.

Primary pulmonary arterial hypertension consists of familial and sporadic cases without underlying connective tissue diseases, congenital heart disease, chronic veno-occlusive disease, or other causal entities. Age of onset among women is in the third and fourth decade, and the median survival without treatment is 2.8 years [31,32]. Few studies have evaluated pregnancy outcomes in patients with PPH [32]. These studies have reported high rates of maternal mortality associated with pregnancy ranging from 30–50%, with the highest risk during the first month after delivery [6,21,33]. Our study confirms that women

with PPH have increased risks for complications during pregnancy. Although women with PPH were older than control patients, multivariable analyses demonstrated substantially worse outcomes. More than half of their hospitalizations were for non-delivery indications. In a previous study, the most common reasons for antenatal hospitalizations included increased dyspnea, hemoptysis, syncope, cyanosis, or hypertensive disorders [21]. In our study, in addition to a high rate of antenatal hospitalizations, patients with PPH had an almost 5-fold increase in HTN and substantially increased LOS for deliveries compared with controls.

The racial composition of patients in our study included a higher percentage of minority women with PPH than in a previously reported national registry [16]. While it is possible that the missing race data could explain this discrepancy, it is also possible that white patients had more consistent counseling against pregnancy than minority populations. Given the higher age-adjusted mortality rate in black women compared with white women with PPH in the absence of the physiological stressors of pregnancy [1,2], concerted efforts should be made to counsel PPH patients from all racial groups of the high risks associated with pregnancy.

SCD is an autosomal recessive genetic disorder to the β -globin gene affecting approximately 50,000 Americans [34] without gender predominance. In the 1970s, the median survival time for this disease was 14.3 years; this has increased to nearly 50 years in recent decades largely due to streptococcus pneumonia prophylaxis and better treatment of vaso-occlusive crises [4]. Similarly, pregnancy outcomes in women with SCD in the 1970s were unacceptably high, and those women surviving to the childbearing years were strongly counseled against becoming pregnant [5]. More recently, the maternal death rate has been reduced to less than two percent, and many women are electing to proceed with pregnancies [8]. Previous studies of pregnancy in women with SCD have been limited by retrospective studies at single institutions, or multi-institution cooperative studies that span nearly 10 years to accumulate patients [8]. A single randomized control trial of red cell transfusions during pregnancy evaluated 72 women accumulated over 5 years [35]. Together, these data on pregnancies in women with SCD in the United States have shown young age at pregnancy, numerous antepartum admissions for complications of underlying SCD (pain crises, acute chest crises, infections, and symptomatic anemia), longer hospital stays, and increased rates of IUGR [36–38]. Results from our study confirm these outcomes in a much larger cohort of nearly 4,400 deliveries over three years of observation. Risks of all adverse pregnancy outcomes under study were independently associated with SCD, suggesting that pregnancy outcomes observed at tertiary care centers may be similar to those seen across the US. The early age of pregnancy we found is consistent with other studies of SCD patients in the US [36–38], and may be a reflection of both diagnosis of this genetic disease during childhood before the childbearing years, as well as a concern for early mortality despite improvements in care [4].

Several limitations of the study require discussion. Despite collecting data over three years, there were still very few pregnancies complicated by SSc or PPH. The small numbers of women with SSc and PPH may be a reflection of the rarity of disease, severity of disease, medication use that precludes pregnancy, diagnosis of underlying disease after childbearing is complete, or a small proportion of women who are able or willing to carry a pregnancy to delivery. Certainly, this will be a concern in any study of pregnancy in these populations. One solution to this problem is to increase the period of observation; however, that may introduce bias as temporal trends in the care of these patients may not be captured within the available data.

Other limitations to this study are inherent to all large, administrative databases. We were unable to verify discharge diagnoses for the underlying diseases or pregnancy outcomes under study. Discharge diagnoses were provided by the treating physicians, without standardized application of diagnostic criteria. This could lead to under- or over-reporting of cases. Misclassification of cases may have resulted in the exclusion of women with very mild forms of disease without significant pregnancy complications thereby biasing the results toward worse pregnancy outcomes. More specifically, we were unable to identify specific subsets of underlying disease which may have important prognostic implications for pregnancy. For example, ICD-9 coding does not allow for distinctions between limited and diffuse SSc; and there may be some misclassification between primary or secondary pulmonary hypertension.

Although the overwhelming majority of deliveries and serious perinatal complications to mother and fetus occur in hospital settings, much of obstetrical care of patients occurs in the outpatient setting and is therefore not captured in hospitalization databases. Accordingly, we have no data on early pregnancy losses or elective termination as these are largely evaluated and treated in the outpatient setting. It is probable that we have missed important data on the incidence and potential risk factors for early pregnancy loss as well as data on women who elect to terminate pregnancy for medical or other reasons. Similarly, administrative databases such as the NIS often lack data on other variables of interest, including duration and severity of underlying disease, medication use, parity, prenatal care, and tobacco or alcohol use, that are often documented in outpatient visits but not in final discharge summaries. Therefore we were unable to control for important confounders that are known to be associated with adverse pregnancy outcomes.

Finally, the database does not have unique patient identifiers, thus the unit of analysis is hospitalization rather than patient. To address this issue, we performed separate analyses limited to hospitalizations associated with delivery of an infant, and this did not alter the conclusions drawn from the data. It was assumed that childbirth occurs once during each pregnancy and that each delivery represents data from a separate pregnancy.

Similarly, because there were no unique patient identifiers, there was no way to link maternal to infant records, so information such as birth weight, congenital anomalies, neonatal hospitalization and death, and other infant-specific outcomes could not be evaluated.

In this study we sought to estimate the numbers of women with these relatively uncommon vasculopathic conditions who deliver annually throughout the United States. Despite noted limitations, the strengths of this study rest in the large numbers of pregnancies from an ethnically diverse nationwide sample of hospitalizations available for analysis. We have confirmed previous observations of adverse pregnancy outcomes in women with underlying PPH and SCD; additionally we have found higher rates of pregnancy complications in this population-based sample of pregnant women with SSc than what has been reported at tertiary-care centers. Up to 40% of women in our study were treated in non-teaching hospitals. Women with these vasculopathic conditions require extensive preconceptional counseling about risks of pregnancy; and all pregnancies should be considered high-risk and monitored carefully for signs of complications.

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Table 1

Population estimates by diagnosis

Group	Obstetric Hospitalizations	95% CI	Delivery	95% CI	Cesarean Delivery	95% CI
Control	14.0 Million	13.2 –14.7 Million	11.2 Million	1.06 –1.18 Million	3,499,180	3,293,523–3,704,838
SSc	695	546–845	504	389–619	212	142–283
PPH	407	304–510	182	117–248	105	56–153
SCD	11,928	10,093–13,763	4,352	3,606–5,097	1,936	1,605–2,268

Table 2

Demographics by diagnosis (Delivery-associated hospitalizations)

Variable	SSc	PPH	SCD	Control
Age (mean, SD)	29.7*** (6.2)	31.5*** (5.9)	25.3*** (5.8)	27.5 (6.2)
% white	55	24.2**	3.4*	51.6
% black	13.7	20.7	89.4*	13.7
% Hispanic	17.5	34.5	5.4*	24.7
% Asian	6.3	10.3	03*	5
% Other race	7.5	10.3	1.6*	5
% Diabetes	1.8	2.6	1.0	0.7
% APLA	0.9	0	0.1	0.1
% Renal Failure	0	2.6**	0.5*	0.02

*
p<0.001,**
p<0.01, by Chi square test***
p<0.05, compared to control using ANOVA for multiple comparisons

Table 3

Obstetric outcomes by diagnosis (Delivery-associated hospitalizations)

Group	LOS [†] (mean, SD)	% Hypertensive disorders of pregnancy	% Premature Rupture of Membranes	% Intrauterine Growth Restriction	% Cesarean Delivery
SSc	4.8 *** (5.7)	22.9 *	1.16 *	5.3 *	42.2 ***
PPH	9.5 *** (8.9)	34.2 *	2.5	2.6	57.9 *
SCD	5.3 *** (6.6)	18.9 *	4.4	6.0 *	44.5 *
Control	2.6 (2.1)	8.3	3.7	1.7	31.1

* p<0.001,

** p<0.01,

*** p<0.05, compared to control

[†] Analysis of Variance (ANOVA) for multiple comparisons

Table 4

Multivariate odds ratios for risk of adverse pregnancy outcomes (Delivery-associated hospitalizations) Covariates included maternal age, race/ethnicity, diabetes mellitus, antiphospholipid antibody syndrome, and renal failure

	Antenatal Hospitalization [†]	Hypertensive Disorders	Intrauterine Growth Restriction	Cesarean Delivery	Length of stay [‡]
SSc	1.49 (0.98–2.28)	3.95* (2.38–6.55)	3.67* (1.48–9.10)	1.43 (0.91–2.24)	2.58* (2.06–3.10)
PPH	4.67* (2.88–7.57)	5.62* (2.60–12.15)	1.75 (0.24–12.96)	3.04** (1.61–7.19)	6.60* (5.76–7.44)
SCD	5.56* (5.08–6.09)	1.78* (1.48–2.14)	2.91* (2.16–3.93)	1.70* (1.46–1.95)	2.27* (2.10–2.44)
White	Reference	Reference	Reference	Reference	Reference
Black	1.28* (1.27–1.30)	1.43* (1.41–1.46)	1.30* (1.26–1.34)	0.98* (0.97–0.99)	0.30* (0.28–0.31)
Hispanic	0.95* (0.94–0.96)	0.79* (0.78–0.80)	0.71* (0.69–0.73)	0.99** (0.98–1.00)	–0.18* (–0.19– –0.17)
Asian	0.83* (0.81–0.84)	0.61* (0.59–0.63)	1.10* (1.04–1.15)	0.90* (0.88–0.91)	0.02 (–0.00– 0.03)

* p<0.001,

** p<0.01,

*** p<0.05 compared to control

[†] includes all obstetric hospitalizations

[‡] Linear regression expressed as a β coefficient; cesarean delivery added as additional covariate