OBSTETRICS

Delivery-associated sepsis: trends in prevalence and mortality

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BACKGROUND: Sepsis is a leading cause of pregnancy-related mortality. Previous studies have reported an increased prevalence of sepsis during pregnancy. Despite national campaigns to increase sepsis awareness, there is a lack of pregnancy-specific guidelines.

OBJECTIVE: We aimed to provide updated national estimates of the prevalence and trends of sepsis, sepsis-related in-hospital mortality, and factors associated with in-hospital mortality among women with sepsis at delivery.

STUDY DESIGN: We conducted a serial, cross-sectional analysis using data from the 2002–2015 National Inpatient Sample, the largest publicly available all-payer inpatient database in the United States. We used *International Classification of Diseases, ninth edition, Clinical Modification* diagnosis and procedure codes to identify the study sample of delivery-associated hospitalizations and to capture diagnoses of sepsis (defined as infection with associated end-organ dysfunction). The primary outcome was in-hospital mortality. Obstetric comorbidities and pregnancy-related outcomes were also analyzed. Logistic regression was used to explore factors associated with sepsis during pregnancy and, among those with sepsis, to identify predictors of in-hospital mortality. Joinpoint regression was used to estimate the temporal trends in both sepsis and in-hospital mortality.

RESULTS: Of the more than 55 million delivery-associated hospitalizations, 13,129 women met criteria for sepsis, corresponding to a rate of 2.4 per 10,000 deliveries. This rate increased from 1.2 to 3.7 per 10,000 over the study period, representing an annual increase of 6.6% (95% confidence interval, 4.2–9.1). The highest crude rates of sepsis (per 10,000) were among deliveries paid for by Medicare (14.8), deliveries to women aged 40 years or older (8.0), and deliveries to non-Hispanic black women (4.6). Compared with women without sepsis, women with sepsis had a greater than 10-fold increased prevalence of most selected obstetric comorbidities. One in 11 women with sepsis died prior to discharge, compared with 1 death in every 15,411 deliveries without sepsis. The sepsis-related mortality rate decreased 21.8% each year from 2010 through 2015. Maternal age greater than 40 years and nonprivate insurance demonstrated the highest odds of sepsis-related in-hospital mortality.

CONCLUSION: While rates of delivery-associated sepsis have increased, case fatality has decreased.

Key words: childbirth, infection, in-hospital mortality, maternal death, maternal morbidity, maternal mortality, National Inpatient Sample, pregnancy

Sepsis remains one of the leading causes of severe maternal morbidity and mortality.[1–3] Significant concerns have been raised by the reported increase in the occurrence of pregnancy-related sepsis in recent years. During the time period of 2001–2010, pregnancy-associated sepsis at delivery doubled from 6 per 10,000 in 2001 to 12 per 10,000 in 2010.[4]

An analysis using the data from the National Inpatient Sample demonstrated a 10% per year increase in maternal severe sepsis and sepsis-related death in the United States between 1998 and 2008.[5] There is also a concomitant increase in sepsis-related maternal death such that infections accounted for 12.7% of maternal deaths annually in the United States.[2] Of the 2009 maternal deaths in 2011–2013, 6.2% were secondary to sepsis.[2]

One of the key factors in surviving sepsis is the rapid identification of the disease and prompt initiation of treatment.[6,7] In an effort to improve outcomes and lower the mortality rate, guidelines and bundles have been implemented widely in hospitals in recent years.[6,8,9] Although there have been some reports of success from using these strategies, pregnant women may not experience the yields of these efforts.[10,11]

Because of physiological changes in pregnancy, the diagnosis of sepsis is difficult, and the parameters used in the general population lack specificity for the pregnant woman. Furthermore, there is a lack of specific treatment guidelines that are tailored to pregnancy.[12] Given these challenges, the improvements in sepsis-related mortality in the general population may not be observed among pregnant women.

Therefore, we sought to provide updated national estimates of the prevalence and trends of delivery-associated sepsis and in-hospital mortality.

Materials and Methods

Design, data source, and study sample

We conducted a serial cross-sectional analysis of delivery hospitalizations in the United States among women 15–49 years of age from Jan. 1, 2002, through Sept. 30, 2015, using data from the National Inpatient Sample (NIS).

The NIS, a product of the Healthcare Cost and Utilization Project developed through a federal-state-industry partnership, is the largest publicly available all-payer inpatient database in the United States. Forty-seven states and the District of Columbia currently contribute state-level hospital discharge data to be compiled annually as part of the NIS.

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AJOG at a Glance

Why was this study conducted?

Prior studies have indicated an increased prevalence of sepsis in pregnancy, and it remains as one of the top causes of maternal mortality. There have been nationwide changes in hospital management of sepsis over the past decade. We sought to evaluate the extent to which there has been any changes in sepsis-related maternal death over the same time period.

Key findings

We confirmed an increase in the prevalence of delivery-associated sepsis. However, the case fatality has decreased. Maternal age greater than 40 years and nonprivate insurance were associated with higher odds of in-hospital death among women with delivery-associated sepsis.

What does this add to what is known?

During a time period during which awareness of sepsis has increased and management has improved nationwide, delivery-associated sepsis mortality rates have decreased.

A discharge is synonymous with a hospitalization, and we will use the latter term from this point forward. Although the sampling strategy was redesigned over time, the NIS ultimately approximates a 20% representative sample of hospitalizations from nonfederal community hospitals and includes hospitalization-level sampling weights to facilitate generation of national estimates of the prevalence and trends of inpatient conditions and procedures.[13]

The redesign of the NIS in 2012 was expected to cause a 1-time 1.3% decrease in mortality rates among patients 18–44 years old; therefore, new trend hospitalization-level weights were developed for pre-2012 databases to make mortality and other estimates comparable with the new NIS design. Our analysis incorporates these Healthcare Cost and Utilization Project–supplied trend files to account for changes in the sampling design, ensure consistency of sampling weights over time, and standardize covariate definitions across the study period.[14]

The NIS contains patient and hospital information pertaining to each hospitalization, including variables containing *International Classification of Diseases, ninth edition, Clinical Modification* (ICD-9-CM) codes capturing the principal diagnosis, up to 29 secondary diagnoses, and diagnostic and therapeutic procedures performed. We excluded hospitalizations during the fourth quarter of 2015 to remove the potential impact on study results of the transition from ICD-9-CM to ICD-10-CM for coding of diagnoses and procedures. Because no personal identifiers are included with the NIS, hospitalizations for the same person cannot be linked over time; therefore, the unit of analysis in NIS-based studies is the hospitalization, not the person.

Sepsis, obstetric comorbidities, and in-hospital mortality

The study sample consisted of delivery hospitalizations of women aged 15–49 years identified by a commonly used algorithm developed by Kuklina et al[15] based on ICD-9-CM diagnoses and procedures and the assigned diagnosis-related group. We did not exclude deliveries associated with ectopic, molar, and other pregnancies with an abortive outcome.

For each delivery hospitalization, the presence of sepsis was defined using an adapted version of an ICD-9-based definition proposed by Bauer et al,[16] which required a diagnosis (principal or secondary) of both disseminated infection/sepsis and acute dysfunction of coagulation or of the central nervous, pulmonary, cardiovascular, renal, or hepatic systems (Supplemental Table 1).

The study's primary outcome was in-hospital mortality, defined as death prior to discharge from the hospitalization in which delivery occurred. In addition, we used ICD-9-CM codes to capture information on 24 conditions that, along with maternal age, have been used to calculate a weighted obstetric comorbidity index. This index has been demonstrated to have an ability to predict severe maternal morbidity (which includes sepsis) and mortality as good or better than other commonly used comorbidity indices for the general population (eg, Elixhauser or Charlson index).[17]

These conditions and behaviors included the following (in alphabetical order): alcohol abuse, asthma, cardiac valvular disease, chronic congestive heart failure, chronic ischemic heart disease, chronic renal disease, congenital heart disease, cystic fibrosis, drug abuse, gestational hypertension, gestational diabetes mellitus, HIV, mild or unspecified preeclampsia, multiple gestation, obesity, placenta previa, previous cesarean delivery, preexisting diabetes mellitus, preexisting hypertension, pulmonary hypertension, severe preeclampsia or eclampsia, sickle cell disease, systemic lupus erythematosus, tobacco use.

We also used ICD-9-CM procedure codes to distinguish between cesarean and vaginal deliveries. The operational definitions for these conditions and procedures is presented in Supplemental Table 1.

Other sociodemographic, clinical, and hospital covariates

The NIS databases also include selected patient sociodemographic and clinical characteristics as well as information about the hospital of care. Patient age in years was categorized as less than 20, four 5-year intervals between 20 and 39, and 40 or older. Race/ethnicity was first defined by reported ethnicity, Hispanic or non-Hispanic. The non-Hispanic group was then further subdivided by documented race: white, black, Asian/Pacific Islander, Native American, and other. Those with missing ethnicity and those in the non-Hispanic group with missing race were classified as unknown.

As a proxy for community-level socioeconomic status, ZIP code level estimates of median household income based on the patient's residence, which has been shown to be independently associated with adverse health outcomes including mortality, were grouped into quartiles.[18]

We grouped the primary payer for the delivery hospitalization into 4 categories: Medicare, Medicaid, private (commercial carrier, private health maintenance organization, and preferred provider organization), and other sources (eg, self-pay and charity). Because weekend, compared with weekday, admission has been reported to be associated with increased inpatient mortality, we also considered timing of admission in our analyses.[19] Hospital characteristics included US Census region (Northeast, Midwest, South, or West), bed size (small, medium, or large), and type (rural, urban nonteaching, or urban teaching).

Statistical analysis

Descriptive statistics including frequencies and percentages were used to describe differences in the distribution of sociodemographic and clinical characteristics between delivery hospitalizations with and without a coded diagnosis of sepsis. Within each subgroup of the study sample, we calculated the rate of delivery-associated sepsis as the number of delivery hospitalizations with a sepsis diagnosis per 10,000 deliveries.

To describe differences in the comorbidity burden, we also compared rates of the 24 obstetric comorbidities, as well as the distribution of obstetric comorbidity index scores, by sepsis status. Multivariable logistic regression was used to generate adjusted odds ratios (OR) and 95% confidence intervals (CI) representing the association between various sociodemographic and clinical characteristics and the likelihood of sepsis at delivery.

Then we also used logistic regression to explore factors associated with the odds of in-hospital mortality specifically among women who experienced delivery-associated sepsis. Because the NIS does not contain identifiers that permit the linkage of multiple hospitalizations for the same patient, by including the linkage of hospitalizations in which a transfer has occurred, we may fail to capture important comorbidities and outcomes such as in-hospital mortality when transfers occur. Moreover, the likelihood of a transfer is substantially higher in sepsis-related deliveries than deliveries without sepsis. Therefore, as a sensitivity analyses, we re-ran all models on a subset of the study sample in which there was no indication of a transfer.

We used joinpoint regression to assess 14 year temporal trends in the rate of delivery-associated sepsis and in in-hospital mortality among deliveries with and without sepsis. Joinpoint regression is specifically designed to detect statistically significant changes in the rates of events over time. It does so by first assuming observed annual rates follow a straight line (a model with zero joinpoints). Then, in an iterative process, joinpoints are added to the model, 1 at a time, and a Monte Carlo permutation test is used to assess the extent to which the added joinpoint improves model fit.[20]

In the best-fitting model, each joinpoint represents a statistically significant change in the trend and is characterized using an annual percent change (APC) with 95% CI. Also, the average APC is calculated. The average APC weights the APCs for each time interval to produce a single number that best describes the trend of each outcome over the entire study period.

Statistical analyses were performed with SAS, version 9.4 (SAS Institute, Inc., Cary, NC) and the Joinpoint Regression Program, version 4.1.1.3 (National Cancer Institute, Bethesda, MD). Statistical tests were 2 sided with a 5% type I error rate. Because NIS data are publicly available and deidentified, this study was classified as exempt by both the University of South Florida and Baylor College of Medicine Institutional Review Boards.

Results

Rate and temporal trends of delivery-associated sepsis

Of the more than 55 million delivery hospitalizations during the 14-year study period, 13,124 women met the criteria for sepsis, corresponding to 1 case of sepsis in every 4196 deliveries, or a rate of 2.4 per 10,000 delivery hospitalizations. The temporal trend in the prevalence of sepsis during pregnancy is displayed in Figure 1. The rate increased from 1.2 per 10,000 (95% CI, 1.0−1.5) to 3.7 per 10,000 (95% CI, 3.2−4.2) between 2002 and 2015. Joinpoint regression analyses estimated a statistically significant average annual increase of 6.6% (95% CI, 4.2−9.1).

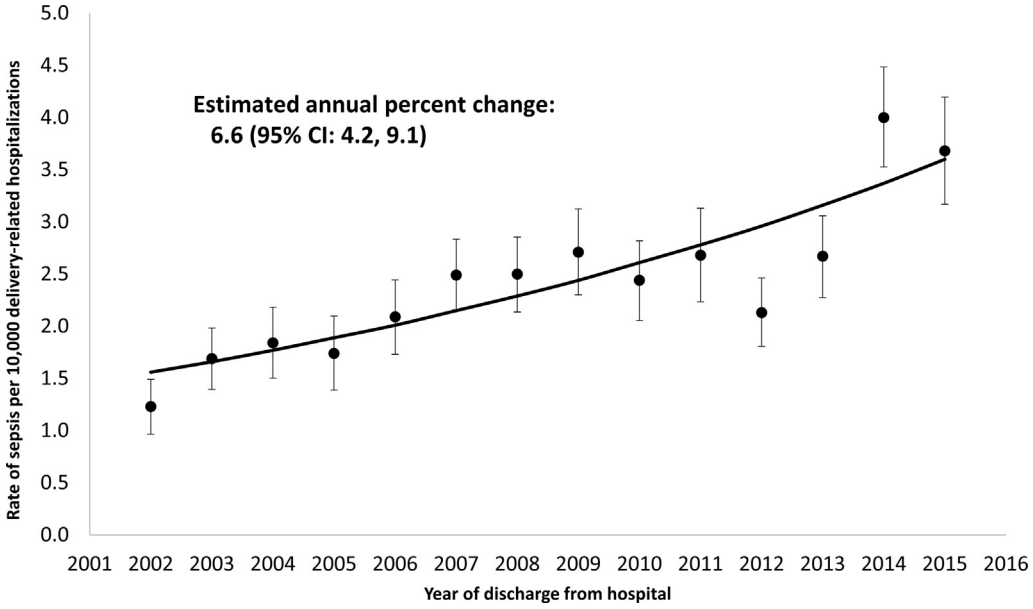
Sociodemographic characteristics associated with a sepsis diagnosis at delivery

Table 1 presents sociodemographic and clinical characteristics for mothers with vs without sepsis and the results of the adjusted association between each characteristics and sepsis. The highest crude rates of sepsis (per 10,000) were among deliveries paid for by Medicare (14.8), deliveries to women aged 40 years or older (8.0), and deliveries to black women (4.6). Some of the lowest rates were among deliveries to white women (1.9), to women with private insurance (1.7), and to women living in high-income areas (1.9).

After adjusting for sociodemographic, clinical, and hospital-level confounders, a number of characteristics were associated with an increased odds of sepsis. Increasing maternal age was associated with an increasing likelihood of sepsis, and women 40 years old and older were 3.5 times more likely to be diagnosed with sepsis compared with women 25−29 years old (95% CI, 2.96−4.04). Compared with whites, blacks and Asian/Pacific Islanders had a 49% and 43% increased odds of sepsis, respectively. The odds of sepsis tended to increase with decreasing household income; compared with women with in the fourth quartile of ZIP code level median household income, women in the first quartile were 1.28 times more likely to have sepsis (95% CI, 1.12−1.47).

Compared with women with private insurance at the time of delivery, women with Medicare, Medicaid, and other insurance experienced 3-fold, 1.6-fold, and 2-fold increased odds of sepsis,

FIGURE 1
Temporal trends in rate of sepsis, 2002–2015



Temporal trends in the rate of sepsis, per 10,000 delivery hospitalizations, 2002–2015, National Inpatient Sample, are shown. This figure describes the temporal trends in sepsis at delivery during the 14 year study period. The Y-axis refers to the sepsis rate per 10,000 delivery hospitalizations. The X-axis refers to the year of discharge from the delivery hospitalization. *Circular markers* depict observed annual rates; error bars represent the 95% confidence intervals; the *solid line* represents the joinpoint regression-estimated trend.

APC, annual percent change, expressed as the point estimate (95% confidence interval).

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respectively. Admission to delivery during the weekend was associated with a 44% greater likelihood for sepsis compared with admission during the weekday, and women who delivered by cesarean delivery were twice as likely to experience sepsis.

Hospital size and type were associated with increased odds of sepsis; women delivering in a large hospital were 1.63 times more likely to have sepsis compared with women delivering in a small hospital (95% CI, 1.40–1.90), and women delivering in an urban teaching hospital were 3 times more likely to have sepsis (95% CI, 2.45–3.72).

Obstetric comorbidities associated with sepsis

Table 1 also summarizes the rates of obstetric comorbidities by the presence of sepsis. In all except 5 of the 24 comorbidities (gestational hypertension, gestational diabetes mellitus, mild or unspecified preeclampsia, placenta previa, and previous cesarean delivery), the rate of the comorbidity was higher among women with sepsis diagnosed at delivery. Compared with women without sepsis, those with sepsis had greater than 10-fold increased prevalence rates of alcohol abuse, chronic ischemic heart disease, chronic renal disease, cystic fibrosis, HIV, pulmonary hypertension, and lupus. This translated into deliveries with sepsis having a distribution of weighted obstetric comorbidity index scores shifted toward higher values; only 5.5% of nonsepsis deliveries had scores of 3 or higher, compared with greater than 25% of sepsis-related deliveries (Supplemental Figure).

Even after adjusting for patient and hospital characteristics, including other obstetric comorbidities, most comorbidities were associated with an increased likelihood of sepsis at delivery, with adjusted ORs more than 5 in magnitude for chronic renal disease (OR, 17.46; 95% CI, 14.47–21.06), cystic fibrosis (OR, 10.79; 95% CI, 3.12–37.35), pulmonary hypertension (OR, 8.61; 95% CI, 5.00–14.85), and chronic congestive heart failure (OR, 5.44; 95% CI, 2.26–13.06).

Rate and trend of delivery-associated mortality

Overall, 1 in 11 women with sepsis at delivery died prior to discharge, compared with 1 death in every 15,411 deliveries without sepsis (Supplemental Table 2). There was a steady decline in the in-hospital mortality rate among women without sepsis, from 0.96 to 0.43 per 10,000 between 2002 and 2015 (annual rate decrease, −5.7%, 95% CI, −7.3 to −4.1) (Figure 2). Among sepsis-related deliveries, from 2002 through 2010, the mortality rate had high variability with no significant trend; however, since 2010 a pronounced and statistically significant 21.8% annual decrease (95% CI, −35.9 to −4.5) in the mortality rate was observed (Figure 3).

TABLE 1
Distribution of sociodemographic and clinical characteristics, rate of sepsis, and association between each characteristic and sepsis among delivery hospitalizations in the United States, 2002–2015, National Inpatient Sample

	Sepsis		No sepsis			Adjusted model 1 Full sample sepsis[b]	Adjusted model 2 Excluding transfers[c]
Characteristics	n[a]	%[a]	n[a]	%[a]	Rate of sepsis per 10,000 deliveries	OR (95% CI)	OR (95% CI)
All discharges	13,124	100.0	55,048,475	100.0	2.4 (2.3, 2.5)	NA	NA
Age, y							
<20	1164	8.9	5,014,401	9.1	2.3 (2.0, 2.6)	1.00 (0.85, 1.17)	0.93 (0.78, 1.12)
20–24	2776	21.1	13,144,991	23.9	2.1 (1.9, 2.3)	0.95 (0.85, 1.07)	0.97 (0.85, 1.10)
25–29	3021	23.0	15,283,107	27.8	2.0 (1.8, 2.1)	Reference	Reference
30–34	2943	22.4	13,419,223	24.4	2.2 (2.0, 2.4)	1.16 (1.03, 1.30)[f]	1.15 (1.01, 1.30)[f]
35–39	1967	15.0	6,612,966	12.0	3.0 (2.7, 3.3)	1.54 (1.35, 1.76)[f]	1.60 (1.38, 1.85)[f]
40 or older	1254	9.6	1,573,787	2.9	8.0 (7.0, 9.0)	3.46 (2.96, 4.04)[f]	2.98 (2.49, 3.56)[f]
Race/ethnicity							
White	4507	34.3	23,556,613	42.8	1.9 (1.8, 2.1)	Reference	Reference
Black	2899	22.1	6,255,389	11.4	4.6 (4.2, 5.0)	1.49 (1.32, 1.68)[f]	1.63 (1.43, 1.87)[f]
Hispanic	2330	17.8	10,460,461	19.0	2.2 (2.0, 2.4)	0.97 (0.86, 1.10)	1.12 (0.98, 1.28)
Asian/Pacific Islander	684	5.2	2,325,236	4.2	2.9 (2.4, 3.5)	1.43 (1.18, 1.73)[f]	1.61 (1.30, 1.99)[f]
Native American	115	0.9	332,693	0.6	3.4 (1.8, 5.1)	1.43 (0.89, 2.29)	1.11 (0.63, 1.96)
Other	602	4.6	2,193,823	4.0	2.7 (2.3, 3.2)	1.23 (1.01, 1.49)[f]	1.33 (1.07, 1.66)[f]
Unknown	1988	15.1	9,924,260	18.0	2.0 (1.8, 2.2)	1.08 (0.95, 1.23)	1.07 (0.92, 1.24)
Median household income for residential ZIP code							
First quartile	4289	32.7	14,711,541	26.7	2.9 (2.7, 3.1)	1.28 (1.12, 1.47)[f]	1.20 (1.04, 1.39)[f]
Second quartile	3238	24.7	13,582,348	24.7	2.4 (2.2, 2.6)	1.24 (1.09, 1.41)[f]	1.16 (1.00, 1.33)[f]
Third quartile	2924	22.3	13,364,034	24.3	2.2 (2.0, 2.4)	1.14 (1.00, 1.29)	1.08 (0.93, 1.24)
Fourth quartile	2368	18.0	12,391,539	22.5	1.9 (1.7, 2.1)	Reference	Reference
Unknown	305	2.3	999,014	1.8	3.1 (2.2, 3.9)	1.22 (0.92, 1.63)	1.15 (0.82, 1.60)
Primary payer							
Medicare	487	3.7	329,831	0.6	14.8 (11.5, 18.0)	3.28 (2.55, 4.22)[f]	3.23 (2.41, 4.33)[f]
Medicaid[d]	6498	49.5	22,998,752	41.8	2.8 (2.7, 3.0)	1.57 (1.42, 1.73)[f]	1.58 (1.41, 1.77)[f]
Private	4929	37.6	28,259,664	51.3	1.7 (1.6, 1.9)	Reference	Reference
Other[e]	1209	9.2	3,460,228	6.3	3.5 (3.0, 3.9)	2.05 (1.77, 2.36)[f]	2.19 (1.87, 2.57)[f]
Timing of admission							
Weekday	9766	74.4	44,318,642	80.5	2.2 (2.1, 2.3)	Reference	Reference
Weekend	3358	25.6	10,729,816	19.5	3.1 (2.9, 3.4)	1.44 (1.32, 1.57)[f]	1.44 (1.31, 1.60)[f]
Cesarean delivery	5898	44.9	17,193,307	31.2	3.4 (3.2, 3.6)	2.08 (1.89, 2.28)[f]	2.18 (1.96, 2.42)[f]
Obstetric comorbidities							
Alcohol abuse	177	1.4	63,976	0.1	27.6 (18.3, 36.8)	2.74 (1.84, 4.08)[f]	1.99 (1.18, 3.35)[f]
Asthma	756	5.8	1,640,026	3.0	4.6 (3.9, 5.4)	1.29 (1.09, 1.54)[f]	1.28 (1.04, 1.57)[f]
Cardiac valvular disease	311	2.4	241,842	0.4	12.8 (9.6, 16.0)	3.00 (2.15, 4.21)[f]	2.78 (1.86, 4.17)[f]
Chronic congestive heart failure	69	0.5	1468	<0.1	446.7 (217.6, 675.7)	5.44 (2.26, 13.06)[f]	5.29 (1.86, 15.04)[f]

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(continued)

TABLE 1
Distribution of sociodemographic and clinical characteristics, rate of sepsis, and association between each characteristic and sepsis among delivery hospitalizations in the United States, 2002–2015, National Inpatient Sample
(continued)

	Sepsis		No sepsis			Adjusted model 1 Full sample sepsis[b]	Adjusted model 2 Excluding transfers[c]
Characteristics	n[a]	%[a]	n[a]	%[a]	Rate of sepsis per 10,000 deliveries	OR (95% CI)	OR (95% CI)
Chronic ischemic heart disease	35	0.3	10,170	<0.1	34.5 (8.9, 60.1)	0.77 (0.26, 2.30)	0.58 (0.12, 2.74)
Chronic renal disease	1162	8.9	131,668	0.2	87.5 (76.1, 98.9)	17.46 (14.47, 21.06)[f]	17.16 (13.80, 21.33)[f]
Congenital heart disease	91	0.7	46,290	<0.1	19.7 (10.8, 28.5)	2.82 (1.60, 4.95)[f]	2.16 (1.06, 4.41)[f]
Cystic fibrosis	14	0.1	3787	<0.1	36.7 (0.1, 78.2)	10.79 (3.12, 37.35)[f]	9.38 (2.10, 41.97)[f]
Drug abuse	951	7.3	761,145	1.4	12.5 (10.7, 14.3)	3.31 (2.75, 4.00)[f]	3.34 (2.69, 4.14)[f]
Gestational hypertension	199	1.5	1,789,089	3.3	1.1 (0.8, 1.4)	0.45 (0.33, 0.61)[f]	0.52 (0.37, 0.71)[f]
Gestational diabetes mellitus	443	3.4	3,046,117	5.5	1.5 (1.2, 1.8)	0.49 (0.40, 0.61)[f]	0.53 (0.42, 0.67)[f]
Human immunodeficiency virus	184	1.4	62,477	0.1	29.4 (20.2, 38.6)	3.91 (2.74, 5.57)[f]	3.22 (2.04, 5.07)[f]
Mild or unspecified preeclampsia	252	1.9	1,212,692	2.2	2.1 (1.5, 2.7)	0.74 (0.56, 0.98)[f]	0.81 (0.60, 1.11)
Multiple gestation	430	3.3	988,570	1.8	4.3 (3.5, 5.2)	1.10 (0.89, 1.37)	1.21 (0.95, 1.54)
Obesity	999	7.6	1,911,146	3.5	5.2 (4.5, 6.0)	1.27 (1.07, 1.50)[f]	1.31 (1.09, 1.58)[f]
Placenta previa	179	1.4	298,294	5.4	6.0 (4.0, 8.0)	1.54 (1.10, 2.16)[f]	1.89 (1.34, 2.65)[f]
Previous cesarean delivery	1200	9.2	8,523,878	15.5	1.4 (1.2, 1.6)	0.31 (0.27, 0.36)[f]	0.33 (0.28, 0.38)[f]
Preexisting diabetes mellitus	849	6.5	524,253	1.0	16.2 (13.7, 18.7)	2.36 (1.91, 2.91)[f]	2.21 (1.74, 2.81)[f]
Preexisting hypertension	1090	8.3	1,053,544	1.9	10.3 (9.0, 11.7)	1.30 (1.08, 1.58)[f]	1.19 (0.95, 1.49)
Pulmonary hypertension	217	1.7	10,575	<0.1	201.0 (135.6, 266.5)	8.61 (5.00, 14.85)[f]	11.31 (6.23, 20.56)[f]
Severe preeclampsia/ eclampsia	1125	8.6	763,044	1.4	14.7 (12.8, 16.6)	3.33 (2.87, 3.88)[f]	3.68 (3.11, 4.36)[f]
Sickle cell disease	163	1.2	83,905	0.2	19.4 (12.5, 26.3)	3.94 (2.71, 5.73)[f]	3.79 (2.48, 5.79)[f]
Systemic lupus erythematosus	186	1.4	59,373	0.1	31.2 (21.8, 40.7)	2.08 (1.41, 3.06)[f]	2.34 (1.53, 3.58)[f]
Tobacco use	988	7.5	2,577,078	4.7	3.8 (3.3, 4.4)	1.06 (0.90, 1.26)	1.10 (0.91, 1.34)
Hospital size							
Small	1005	7.7	6,548,018	11.9	1.5 (1.3, 1.8)	Reference	Reference
Medium	3012	22.9	14,885,256	27.0	2.0 (1.8, 2.2)	1.23 (1.04, 1.46)[f]	1.28 (1.06, 1.55)[f]
Large	9056	69.0	33,393,077	60.7	2.7 (2.6, 2.9)	1.63 (1.40, 1.90)[f]	1.62 (1.36, 1.93)[f]
Hospital type							
Rural	552	4.2	6,169,458	11.2	0.9 (0.7, 1.1)	Reference	Reference
Urban, nonteaching	4060	30.9	22,051,149	40.1	1.8 (1.7, 2.0)	2.20 (1.78, 2.71)[f]	2.00 (1.59, 2.52)[f]
Urban, teaching	8460	64.5	26,605,743	48.3	3.2 (3.0, 3.4)	3.02 (2.45, 3.72)[f]	2.52 (2.01, 3.17)[f]
Year of discharge							
2002–2011	8694	66.2	40,708,292	73.9	2.1 (2.0, 2.3)	Reference	Reference
2012–2014	4430	33.8	14,340,184	26.1	3.1 (2.9, 3.3)	1.27 (1.15, 1.39)[f]	1.27 (1.15, 1.41)[f]

CI, confidence interval; *OR* odds ratio.

[a] Weighted to estimate national frequency; sum of all groups may not add up to the total because of missing data. Percentages are column percentages to show the distribution of that characteristic in the 2 sepsis groups; [b] Model was run on all delivery-related hospitalizations and was adjusted for all of the variables listed in the table; [c] Model was run on a subset of delivery-related hospitalizations in which there was no indication of a hospital transfer and was adjusted for all of the variables listed in the table. This subset excluded 22.8% and 1.0% of transfer-associated deliveries with and without an indication of sepsis, respectively; [d] Reproductive-aged women on Medicare are often disabled or have renal failure, and the absolute number is small; [e] Includes self-pay, no charge, and other payers; [f] Odds ratios statistically significantly different from 1 (ie, 95% confidence intervals that do not contain 1.00).

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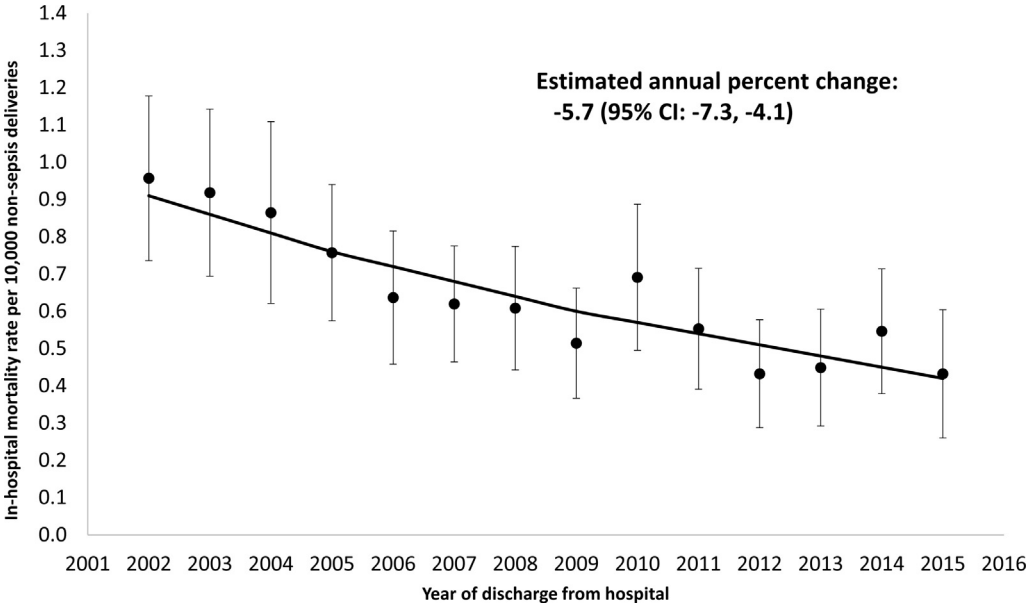
FIGURE 2
Temporal trends of in-hospital mortality without sepsis, 2002–2015



Temporal trends in the rate of in-hospital mortality, per 10,000 delivery hospitalizations without an indication of sepsis, 2002–2015, National Inpatient Sample, are shown. This figure describes the temporal trends in mortality prior to discharge during the 14 year study period among delivery hospitalizations in which there was no indication of sepsis. The Y-axis refers to the in-hospital mortality rate per 10,000 non-sepsis delivery hospitalizations. The X-axis refers to the year of discharge from the delivery hospitalization. *Circular markers* depict observed annual rates; error bars represent the 95% confidence intervals; the *solid line* represents the joinpoint regression-estimated trend.

APC, annual percent change, expressed as the point estimate (95% confidence interval).

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Factors associated with in-hospital mortality among women with delivery-associated sepsis

After controlling for sociodemographic, clinical, and hospital-level confounders, factors associated with increased odds of in-hospital death among women with sepsis at delivery were maternal age 40 years or older (OR, 2.25, 95% CI, 1.37–3.68), women on Medicaid (OR, 1.53, 95% CI, 1.09–2.15), and women with cystic fibrosis, HIV, and pulmonary hypertension (Table 2). Women with sepsis-related deliveries who were younger than 20 years had a statistically significant 52% decreased likelihood of death compared with women 25-29 years.

Sensitivity analyses

Approximately 23% of women with a sepsis-associated delivery and 1% of women without sepsis at delivery had an indication of a hospital transfer taking place. To ensure the inclusion of transfers into our study did not have an impact on our findings, we re-ran all models on a subset of the study sample in which there was no indication of a transfer. Although there were differences in the estimated measures of association, any conclusions based on these models would be identical to those indicated by our sepsis and mortality models on the full sample of all deliveries.

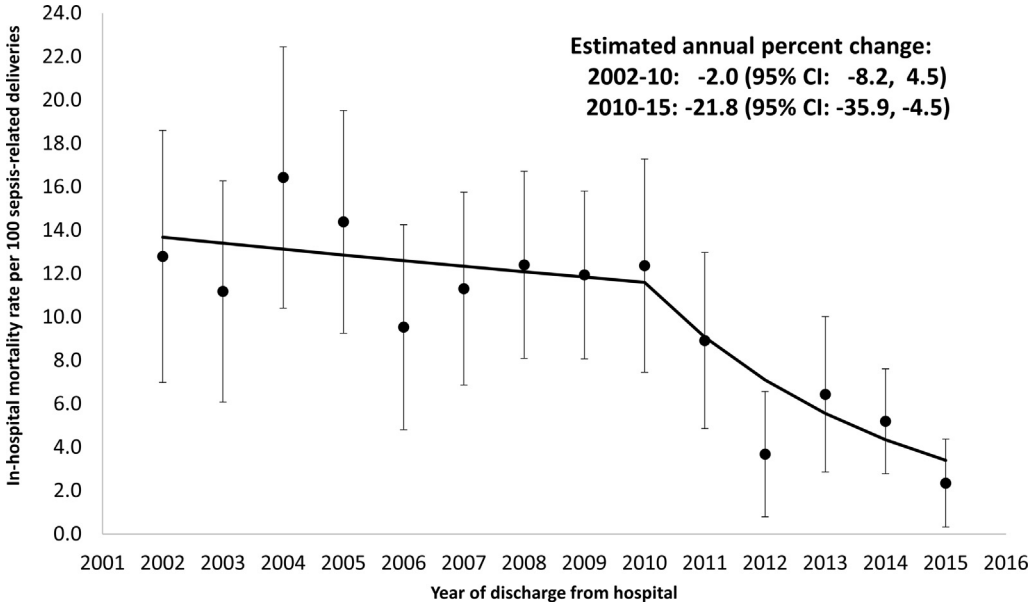
Comment

In an analysis of more than 55 million delivery-associated hospitalizations, we observed an increase in the rate of delivery-associated sepsis over a 14 year study period. However, the rate of sepsis-related in-hospital maternal mortality declined significantly during the last 6 years of the study. Patients older than age 40 years, insured by Medicaid, or with comorbidities were more likely to die prior to discharge.

The increase in maternal mortality rates in the United States, at a time when rates are improving in other parts of the world, has been a source of frustration and increased focus for intervention in recent years.[2,21,22] Analysis of the top causes of maternal deaths includes sepsis.[2] The findings from this study showing an increase in the prevalence of pregnancy-related sepsis are consistent with previous studies.[5,16]

It is uncertain whether the rise in sepsis represents a true increase as opposed to improved recognition and coding. Increased awareness of sepsis may lead to earlier consideration of the diagnosis and coding the encounter accordingly. Also, increases in the sepsis rate in the general population have been found to occur following the introduction of Centers for Medicare and Medicaid Services issued guidance for sepsis ICD-9 coding. We cannot ignore the potential of those policies to explain, at least in part, the observed increased prevalence in this study.[23]

FIGURE 3
Temporal trends of in-hospital mortality with sepsis, 2002–2015



Temporal trends in the rate of in-hospital mortality, per 100 delivery hospitalizations with an indication of sepsis, 2002–2015, National Inpatient Sample, are shown. This figure describes the temporal trends in mortality prior to discharge during the 14 year study period among delivery hospitalizations in which there was an indication of sepsis. The Y-axis refers to the in-hospital mortality rate per 100 sepsis-related delivery hospitalizations. The X-axis refers to the year of discharge from the delivery hospitalization. *Circular markers* depict observed annual rates; error bars represent the 95% confidence intervals; the *solid line* represents the joinpoint regression-estimated trend.

APC, annual percent change, expressed as the point estimate (95% confidence interval).

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One of the most significant obstacles to capturing the true burden of delivery-associated sepsis has been interpreting adult sepsis criteria in the context of pregnancy. Normal physiological changes in pregnancy frequently mimic parameters suggestive of infection.[23,24] As such, in the presence of maternal infection, it is difficult to distinguish normal alterations in vital signs, acid-base status, and laboratory markers from hallmark signs of sepsis.

Studies investigating the utility of sepsis screening tools such as systemic inflammatory response syndrome, quick sequential organ failure assessment, and maternal early warning system in the pregnant population have reported a wide variation in the sensitivity and specificity for the detection of sepsis.[23,25] Additionally, no definitive source of infection is identified in 30% of pregnancy-associated sepsis.[26] This diagnostic challenge introduces the possibility of both over- and underestimation of the rate of sepsis.

Despite the challenges in identifying and treating sepsis in obstetric populations, it would appear that the mortality rate is improving.[27] The rate of sepsis-related maternal mortality was noted to drop quite precipitously from 2010 to 2015, with an annual percentage decrease of 21.8% in our study. In the general population, sepsis is associated with a high mortality rate and prompt identification and treatment can have an impacton outcome.[6,10] Guidelines and bundles emphasize the importance of early initiation of antibiotics and treatment.[6,7]

The launch of the Surviving Sepsis Campaign occurred during our study period, with the initial release of the *Implementing the Surviving Sepsis Campaign* manual in 2005. Included within were bundles with actionable and time-sensitive items including initiation of antibiotics and fluid resuscitation. The data from this international, multicenter study were released in 2010, demonstrating increasing hospital compliance with bundles and simultaneous significant decreases in hospital mortality. The latter finding coincides with the decreased rates of maternal mortality noted in our analysis.[6]

The decreasing trend we observed in this study among pregnant women with and without sepsis mirrors what has been observed in the general population.[10,11] Although this is reassuring, more detailed patient level investigations may be needed to identify the necessary steps to further improve outcomes of delivery-associated sepsis.

In addition to the decline in sepsis mortality rates, our study demonstrates an overall decline in maternal mortality during the study period. While this is contrary to other national data, it is important to recognize that the decline

TABLE 2
Factors associated with in-hospital mortality among delivery hospitalizations with a diagnosis of sepsis, 2002–2015, National Inpatient Sample

Characteristics	In-hospital mortality rate per 100 deliveries	Adjusted model 1 Full sample with sepsis[a] OR (95% CI)	Adjusted model 2 Excluding transfers[b] OR (95% CI)
All discharges	9.4 (8.3, 10.6)	NA	NA
Age, y			
<20	5.2 (2.5, 7.9)	0.48 (0.25, 0.93)[d]	0.48 (0.21, 1.07)
20–24	8.5 (6.2, 10.8)	0.95 (0.62, 1.47)	0.93 (0.57, 1.50)
25–29	8.7 (6.4, 11.0)	Reference	Reference
30–34	7.9 (5.6, 10.2)	1.00 (0.66, 1.52)	1.07 (0.65, 1.73)
35–39	11.4 (8.4, 14.5)	1.40 (0.91, 2.15)	1.35 (0.83, 2.20)
40 or older	17.8 (13.1, 22.5)	2.25 (1.37, 3.68)[d]	2.58 (1.45, 4.58)[d]
Race/ethnicity			
White	9.1 (7.3, 11.0)	Reference	Reference
Black	11.9 (9.0, 14.8)	1.04 (0.69, 1.57)	1.13 (0.71, 1.78)
Hispanic	7.2 (5.0, 9.5)	0.67 (0.44, 1.03)	0.65 (0.40, 1.06)
Asian/Pacific Islander	5.6 (2.0, 9.1)	0.60 (0.27, 1.33)	0.50 (0.20, 1.26)
Native American	Suppressed[c]	0.61 (0.11, 3.32)	1.68 (0.30, 9.29)
Other	9.3 (4.4, 14.1)	0.95 (0.50, 1.80)	0.69 (0.32, 1.51)
Unknown	10.7 (7.5, 13.9)	0.85 (0.56, 1.29)	0.70 (0.43, 1.13)
Median household income for residential ZIP code			
First quartile	10.4 (8.3, 12.4)	1.20 (0.76, 1.88)	1.26 (0.74, 2.13)
Second quartile	9.5 (7.3, 11.7)	1.22 (0.78, 1.92)	1.62 (0.96, 2.71)
Third quartile	9.7 (7.4, 12.1)	1.30 (0.83, 2.04)	1.39 (0.83, 2.34)
Fourth quartile	7.6 (5.2, 9.9)	Reference	Reference
Primary payer			
Medicare	17.4 (10.3, 24.5)	1.58 (0.83, 3.02)	2.02 (0.94, 4.35)
Medicaid	10.0 (8.3, 11.7)	1.53 (1.09, 2.15)[d]	1.61 (1.11, 2.35)[d]
Private	7.6 (6.0, 9.1)	Reference	Reference
Other	11.0 (7.3, 14.7)	1.57 (0.99, 2.47)	1.54 (0.91, 2.58)
Timing of admission			
Weekday	9.8 (8.4, 11.1)	Reference	Reference
Weekend	8.5 (6.4, 10.6)	0.87 (0.63, 1.19)	0.83 (0.57, 1.19)
Cesarean delivery	8.5 (6.8, 10.1)	0.99 (0.72, 1.36)	0.90 (0.63, 1.28)
Obstetric comorbidities			
Alcohol abuse	24.9 (9.5, 40.2)	2.64 (0.97, 7.24)	2.98 (0.84, 10.53)
Asthma	6.9 (3.0, 10.8)	0.79 (0.40, 1.56)	0.76 (0.35, 1.66)
Cardiac valvular disease	9.4 (2.2, 16.5)	0.73 (0.27, 1.95)	0.55 (0.13, 2.22)
Chronic congestive heart failure	Suppressed[c]	0.95 (0.17, 5.24)	1.27 (0.31, 5.23)
Chronic ischemic heart disease	Suppressed[c]	0.83 (0.11, 6.49)	1.50 (0.16, 13.96)
Chronic renal disease	11.9 (7.6, 16.3)	1.46 (0.89, 2.38)	1.60 (0.89, 2.88)

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TABLE 2
Factors associated with in-hospital mortality among delivery hospitalizations with a diagnosis of sepsis, 2002–2015, National Inpatient Sample *(continued)*

Characteristics	In-hospital mortality rate per 100 deliveries	Adjusted model 1 Full sample with sepsis[a] OR (95% CI)	Adjusted model 2 Excluding transfers[b] OR (95% CI)
Congenital heart disease	Suppressed[c]	0.91 (0.15, 5.44)	2.12 (0.34, 13.17)
Cystic fibrosis	Suppressed[c]	28.17 (1.97, 402.99)[d]	13.41 (0.91, 196.78)
Drug abuse	11.6 (7.0, 16.2)	1.38 (0.79, 2.38)	1.10 (0.55, 2.23)
Gestational hypertension	7.3 (0.1, 15.3)	1.06 (0.29, 3.96)	1.23 (0.33, 4.61)
Gestational diabetes mellitus	7.4 (2.2, 12.7)	0.87 (0.38, 2.00)	0.76 (0.30, 1.95)
Human immunodeficiency virus	35.6 (22.2, 48.9)	4.04 (1.76, 9.28)[d]	5.78 (2.03, 16.46)[d]
Mild or unspecified preeclampsia	Suppressed[c]	0.43 (0.10, 1.93)	0.22 (0.03, 1.76)
Multiple gestation	4.5 (0.2, 8.8)	0.58 (0.20, 1.70)	0.72 (0.24, 2.11)
Obesity	5.4 (2.3, 8.4)	0.63 (0.32, 1.22)	0.67 (0.32, 1.38)
Placenta previa	Suppressed[c]	0.57 (0.12, 2.57)	0.64 (0.14, 3.03)
Previous cesarean delivery	6.3 (3.4, 9.3)	0.71 (0.40, 1.26)	0.73 (0.38, 1.37)
Preexisting diabetes mellitus	11.2 (6.7, 15.6)	1.14 (0.67, 1.96)	1.34 (0.72, 2.47)
Preexisting hypertension	11.0 (6.7, 15.4)	0.93 (0.52, 1.64)	1.00 (0.54, 1.86)
Pulmonary hypertension	19.9 (9.2, 30.5)	2.50 (1.08, 5.78)[d]	2.30 (0.85, 6.23)
Severe preeclampsia/eclampsia	9.3 (5.6, 12.9)	1.05 (0.65, 1.72)	1.26 (0.75, 2.13)
Sickle cell disease	12.1 (1.2, 23.0)	0.91 (0.27, 3.09)	1.11 (0.32, 3.87)
Systemic lupus erythematosus	15.3 (4.0, 26.6)	1.03 (0.36, 2.92)	0.78 (0.21, 2.97)
Tobacco use	5.7 (2.8, 8.7)	0.47 (0.24, 0.93)[d]	0.38 (0.16, 0.94)[d]
Hospital size			
Small	6.8 (3.4, 10.2)	reference	reference
Medium	8.4 (6.0, 10.8)	1.00 (0.51, 1.97)	0.99 (0.47, 2.10)
Large	10.0 (8.6, 11.5)	1.31 (0.70, 2.46)	1.10 (0.55, 2.21)
Hospital type			
Rural	6.6 (2.4, 10.9)	Reference	Reference
Urban, nonteaching	7.9 (6.1, 9.6)	1.21 (0.54, 2.72)	1.17 (0.52, 2.63)
Urban, teaching	10.3 (8.8, 11.9)	1.66 (0.76, 3.66)	1.36 (0.62, 2.99)
Year of discharge			
2002–2011	12.0 (10.4, 13.6)	Reference	Reference
2012–2014	4.5 (3.2, 5.9)	0.34 (0.23, 0.50)[d]	0.31 (0.20, 0.48)[d]

CI, confidence interval; *OR* odds ratio.

[a] Model was run on all sepsis-related delivery-related hospitalizations and was adjusted for all of the variables listed in the table; [b] Model was run on a subset of sepsis-related delivery-related hospitalizations in which there was no indication of a hospital transfer and was adjusted for all of the variables listed in the table; [c] In accordance with data suppression rules established by the Healthcare Cost and Utilization Project, rates based on 10 or fewer events (in this case, in-hospital deaths among sepsis-related deliveries) are suppressed; [d] Odds ratios statistically significantly different from 1 (ie, 95% confidence intervals that do not contain 1.00).

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observed in this study was only for in-hospital delivery-associated mortality. Because the primary outcome analyzed was in-hospital delivery-associated sepsis mortality, this analysis is not comprehensive enough to capture the rates of total, all-cause maternal mortality in the United States: specifically, we do not capture deaths that occurred outside the hospital or on readmission hospitalizations in which a delivery did not occur.

In our study, women aged 40 years and older and women with a moderate obstetric comorbidity burden were at

increased odds of sepsis-related maternal death. Women are delaying childbearing and are starting pregnancy older and with more comorbidity, which can predispose them to maternal complications of labor and delivery.[24,28–31]

These associations have been observed with other causes of maternal morbidity and mortality and further emphasize the need to optimize maternal health prior to pregnancy. Of note, women delivering in large, academic hospital settings were more likely be have sepsis. This can be attributed to these women requiring a hospital setting that is better equipped to handle maternal comorbidity or prematurity, rather than the nature of the hospital itself causing higher rates of sepsis.

In 2016, the Third International Consensus definition for sepsis and septic shock was published.[32] In this definition, the distinction between sepsis and severe sepsis, a concept that was the focus of previous large epidemiological studies, was abolished. In this most recent iteration, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The outlined diagnostic criteria focus largely on quantifiable aberrations in vital signs and laboratory values, specifically as an increased Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score of greater than 2 points from baseline.

Given these new definitions and the relatively infrequent occurrence of delivery-associated sepsis, further studies may be limited. Large retrospective studies will not capture specific enough data to calculate SOFA, and prospective studies will suffer from the rare occurrence. Multicenter studies will be needed.

In our study, we included additional ICD-9 codes to capture delivery hospitalizations that were complicated by both infection and coexisting organ dysfunction. This increases the likelihood that the algorithm is capturing severe cases. Moreover, unlike previous analyses, this one includes molar, ectopic, and abortions, which results in a more comprehensive representation of the burden of sepsis.

Although this study design provides a robust, diverse, and generalizable patient population, the use of the National Inpatient Sample imposes limitations to data interpretation. First, our ability to identify sepsis, co-occurring conditions, and comorbidities at delivery relies exclusively on ICD-9-CM codes with suboptimal validity and reliability; the deidentified nature of the NIS precludes our ability to evaluate the sensitivity and specificity of codes through medical record review. It is thus difficult to distinguish cases in which end-organ damage resulted as a direct consequence of infection or whether it was merely an independent and preexisting factor complicating delivery.

Specific vital sign and laboratory values used to calculate SOFA scores are not available in the NIS database, which would better identify organ dysfunction resulting from infection. The data are also subject to coding inaccuracy because of a tendency of providers to underreport comorbid diagnoses in deliveries that are uncomplicated. Because of the inability to link hospitalizations prior to the delivery hospitalization for each woman, sepsis that occurred in the antepartum period and did not result in an inpatient delivery would be excluded from this analysis.

Additionally, we are unable to capture readmissions or postdelivery encounters during the postpartum period, making our assessment of sepsis-related outcomes restricted to the delivery hospitalization and therefore somewhat limited in scope. Finally, in accounting for the decrease in delivery-associated mortality in our study, there are additional variables that may account for the precipitous decline beginning in 2010.

With evolving definitions of sepsis, it is possible that improved awareness led to the identification of more less severe cases, essentially diluting the pool of women diagnosed. However, we used the same definition of sepsis throughout the study period, and the weighted denominator of delivery-related hospitalizations remained relatively constant, while the weighted number of in-hospital deaths tended to decrease over time. Overall, our model found a mortality rate of 1 in 11 women with delivery-associated sepsis, which is largely consistent with new guidelines that attribute an approximate 10% mortality risk in the setting of infection with increased SOFA score of 2 or greater.[32]

Despite these limitations, our findings from this large, nationally representative study of delivery-associated sepsis in the United States indicate that there has been a decrease in sepsis-related in-hospital maternal deaths. There exists a substantial population of high-risk women with comorbid medical conditions who, especially in the context of coexisting infection, warrant additional clinical scrutiny to avoid additional undue maternal morbidity and mortality. Future prospective studies that focus on prevention strategies and effective treatment in the pregnant population are needed. ■

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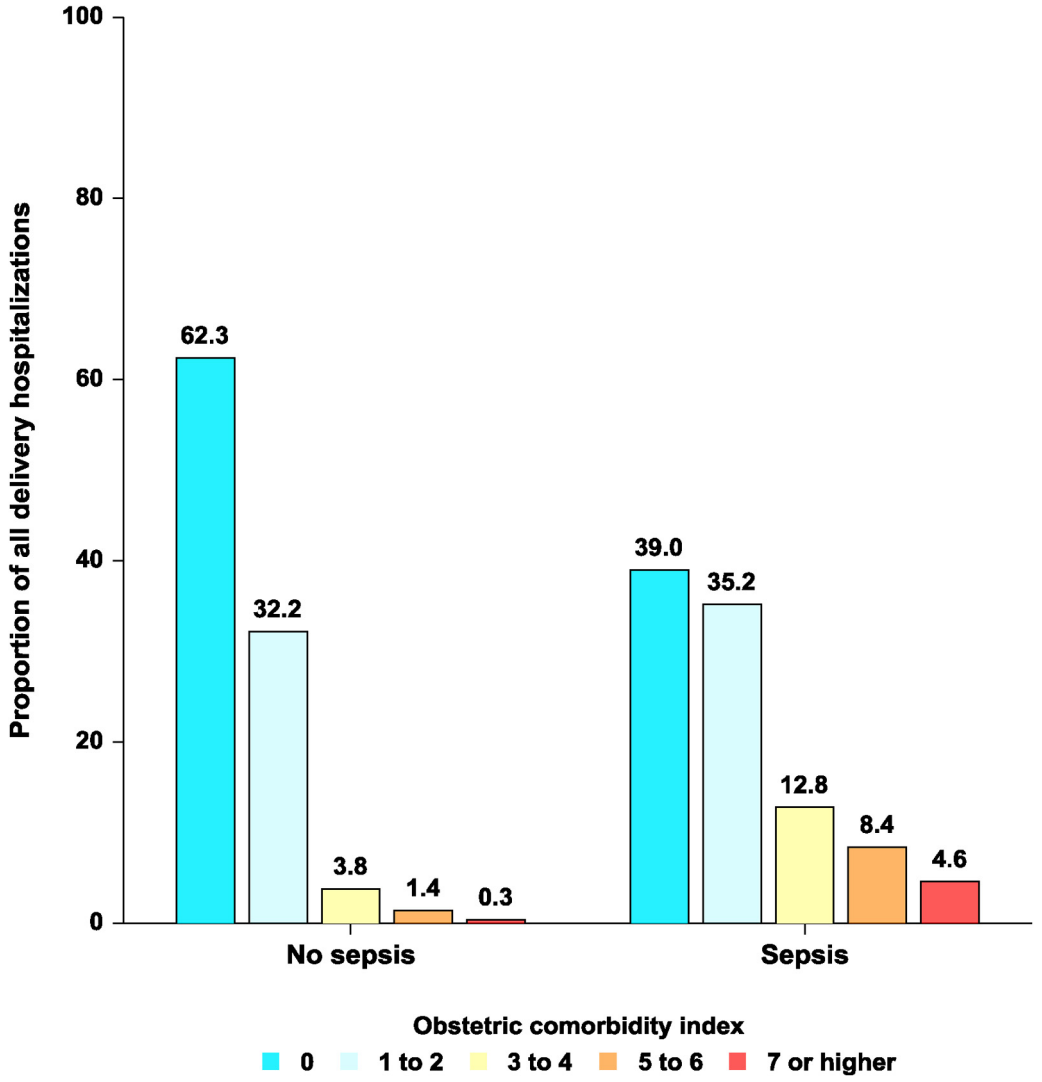
SUPPLEMENTAL FIGURE
Distribution of obstetric comorbidity index, by presence of sepsis, 2002–2015



Distribution of the obstetric comorbidity index, by presence of sepsis, 2002-2015, National Inpatient Sample, is shown.

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SUPPLEMENTAL TABLE 1

List of the *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) diagnosis codes used to identify selected clinical conditions

Condition	ICD-9-CM diagnosis codes[a]
Infection	
Septicemia	038.xx
Disseminated candidiasis	112.5x
Generalized infection during labor	659.3x
Cardiogenic shock	785.52[b]
Sepsis, severe sepsis	995.91, 995.92[c]
Acute organ dysfunction	
Central nervous system	293.0, 348.1, 348.3x, 436, 669.4x, 780.01, 780.03, 997.01
Pulmonary system	518.5x, 518.81, 518.82, 518.84, 786.09, 799.1
Cardiovascular system	410.xx, 415.xx, 427.5, 428.1, 428.21,[d] 428.31,[d] 428.41,[d] 458.0, 458.8, 458.9, 669.1x, 785.5x, 796.3, 997.1, 998.0x
Renal system	584.xx, 669.3x
Hepatic system	570, 572.2, 573.4, 646.7x, 674.8x
Coagulation dysfunction	286.6, 286.9, 587.4x, 666.3x
Obstetric comorbidities	
Alcohol abuse	291.xx, 303.xx, 305.0x Asthma 493.xx
Cardiac valvular disease	394.x-397.x, 424.xx
Chronic congestive heart failure	428.22,[d] 428.23,[d] 428.32,[d] 428.33,[d] 428.42,[d] 428.43[d]
Chronic ischemic heart disease	412, 413.x, 414.xx
Chronic renal disease	581.xx-583.xx, 585.x, 587, 588.xx, 646.2x
Congenital heart disease	745.0xx-747.4x, 648.5x
Cystic fibrosis	277.0x
Drug abuse	304.x, 305.2x-305.9x, 648.3x
Gestational hypertension	642.3x
Gestational diabetes mellitus	648.8x
HIV	042, V08
Mild or unspecified preeclampsia	642.4x
Multiple gestation	V27.2-V27.7, 651.xx
Obesity	278.0x, 649.1x,[e] ,V85.3x,[f] V85.4x[f]
Placenta previa	641.0x, 641.1x
Previous cesarean delivery	654.2x
Preexisting diabetes mellitus	250.xx, 648.0x
Preexisting hypertension	401.x-405.xx, 642.0x-642.2x, 642.7x
Pulmonary hypertension	416.0, 416.8, 416.9

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SUPPLEMENTAL TABLE 1

List of the *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) diagnosis codes used to identify selected clinical conditions *(continued)*

Condition	ICD-9-CM diagnosis codes[a]
Severe preeclampsia or eclampsia	642.5x, 642.6x
Sickle cell disease	282.4x, 282.6x
Systemic lupus erythematosus	710.0
Tobacco use	305.1, 649.0x[e]
Procedures	ICD-9-CM procedure code
Cesarean delivery	74.0-74.4, 74.99

[a] The code suffix x represents all possible codes that follow the stated code prefix. Unless otherwise specified, codes were either available for the entire study period (Jan. 1, 2002, through Sept. 30, 2015) or the operationalization of the code did not change (eg, 518.52 was new on Oct. 1, 2011, but was previously captured by the 518.5x root code); [b] Codes were not available until Oct. 1, 2003; [c] Codes were not available until Oct. 1, 2002, but were previously captured by 038.xx so would have still fit the definition of infection; [d] Codes were not available until Oct. 1, 2002; [e] Codes were not available until Oct. 1, 2006; [f] Codes were not available until Oct. 1, 2005.

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SUPPLEMENTAL TABLE 2

Annual frequencies of the number of deliveries and the number of in-hospital delivery-related deaths, raw and weighted, by sepsis status, 2002–2015, National Inpatient Sample

Variables	Unweighted		Weighted		
	Delivery hospitalizations	In-hospital deaths	Delivery hospitalizations	In-hospital deaths	In-hospital mortality rate (95% CI)[a]
No sepsis					
2002	883,800	85	4,085,394	391	1.0 (0.7, 1.2)
2003	868,064	79	4,021,061	369	0.9 (0.7, 1.1)
2004	893,743	79	4,177,741	361	0.9 (0.6, 1.1)
2005	874,945	68	4,135,899	313	0.8 (0.6, 0.9)
2006	894,876	59	4,211,789	268	0.6 (0.5, 0.8)
2007	945,907	60	4,458,248	276	0.6 (0.5, 0.8)
2008	881,693	56	4,113,597	250	0.6 (0.4, 0.8)
2009	833,581	44	4,002,770	206	0.5 (0.4, 0.7)
2010	789,496	54	3,773,763	261	0.7 (0.5, 0.9)
2011	808,437	47	3,728,030	206	0.6 (0.4, 0.7)
2012	763,414	33	3,817,071	165	0.4 (0.3, 0.6)
2013	757,552	34	3,787,758	170	0.4 (0.3, 0.6)
2014	768,747	42	3,843,735	210	0.5 (0.4, 0.7)
2015[b]	578,324	25	2,891,620	125	0.4 (0.3, 0.6)
Sepsis					
2002	109	14	501	64	12.8 (7.0, 18.6)
2003	147	16	679	76	11.2 (6.1, 16.3)
2004	164	28	770	126	16.4 (10.4, 22.5)
2005	156	22	721	104	14.4 (9.2, 19.5)
2006	188	18	879	84	9.5 (4.8, 14.3)
2007	235	27	1113	126	11.3 (6.9, 15.7)
2008	222	27	1027	127	12.4 (8.1, 16.7)
2009	231	28	1086	130	11.9 (8.1, 15.8)
2010	191	24	919	114	12.4 (7.5, 17.3)
2011	213	19	1000	89	8.9 (4.9, 13.0)
2012	163	Suppressed[c]	815	30	3.7 (0.8, 6.6)
2013	202	13	1010	65	6.4 (2.9, 10.0)
2014	308	16	1540	80	5.2 (2.8, 7.6)
2015[b]	213	Suppressed[c]	1065	25	2.3 (0.3, 4.4)[a]

HCUP, Healthcare Cost and Utilization Project; *ICD-9-CM*, International Classification of Diseases, ninth edition, Clinical Modification; *ICD-10-CM*, International Classification of Diseases, tenth edition, Clinical Modification.

[a] Per HCUP recommendations, the mortality rate was calculated using discharge weights. Because of the rarity of in-hospital mortality among delivery hospitalizations without any indication of sepsis, the mortality rate was expressed as deaths per 10,000 deliveries. Among sepsis-related deliveries, the rate was expressed as the percentage of all delivery-related hospitalizations in which death occurred prior to discharge; [b] In 2015, only delivery-related hospitalizations from Jan. 1, 2015, to Sept. 30, 2015, were included because of the transition from ICD-9-CM coding to ICD-10-CM coding on Oct. 1, 2015. This explains the decrease in all counts relative to previous years; however, the reported rates remain valid as a comparator of mortality to previous years; [c] In accordance with data suppression rules established by the Healthcare Cost and Utilization Project, frequencies of 10 or fewer are supressed.

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