Prepregnancy Risk Factors for Antepartum Stillbirth in the United States

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OBJECTIVE: To identify possible prepregnancy risk factors for antepartum stillbirth and to determine whether these factors identify women at higher risk for term stillbirth.

METHODS: This retrospective cohort study of prepregnancy risk factors compared 712 singleton antepartum stillbirths with 174,097 singleton live births at or after 23 weeks of gestation. The risk of term antepartum stillbirth then was assessed in a subset of 155,629 singleton pregnancies.

RESULTS: In adjusted multivariable analyses, African-American race, Hispanic ethnicity, maternal age 35 years or older, nulliparity, prepregnancy body mass index (BMI) 30 or higher, preexisting diabetes, chronic hypertension, smoking, and alcohol use were independently associated with stillbirth. Prior cesarean delivery and history of preterm birth were associated with increased stillbirth risk in multiparous women. The risk of a term stillbirth for women who were white, 25–29 years old, normal weight, multiparous, no chronic hypertension, and no preexisting diabetes was 0.8 per 1,000. Term stillbirth risk increased with the following conditions: preexisting diabetes (3.1 per 1,000), chronic hypertension (1.7 per 1,000), African-American race (1.8 per 1,000), maternal age 35 years or older (1.3 per 1,000), BMI 30 or higher (1 per 1,000), and nulliparity (0.9 per 1,000).

CONCLUSION: There are multiple independent risk factors for antepartum stillbirth. However, the value of individual risk factors of race, parity, advanced maternal age (35–39 years old), and BMI to predict term stillbirth is poor. Our results do not support routine antenatal surveillance for any of these risk factors when present in isolation.

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LEVEL OF EVIDENCE: II

Stillbirth, defined as fetal death at 20 weeks of gestation or more, is one of the most common adverse pregnancy outcomes in the United States and occurs in one of every 200 pregnancies. The number of stillbirths per year (25,894) is approximately equivalent to the number of infant deaths (28,384) (2005 data).[1] The Healthy People 2010 target goal for the U.S. stillbirth rate is 4.1 fetal deaths per 1,000 births; the current rate, at 6.2 per 1,000 births, is 52% higher than this goal (2005 data).[1]

Factors that have been associated with an increased risk of antepartum stillbirth include previous adverse pregnancy outcomes,[2] advanced maternal age,[3] African-American race,[4] smoking,[5] maternal medical disease such as pregestational diabetes and chronic hypertension,[6] fetal growth impairment,[7] and assisted reproductive technology.[8] The most prevalent independent risk factors are nulliparity,[5] obesity,[9] and advanced maternal age. Women who are obese and those of advanced maternal age constitute an increasingly large proportion of the obstetric population and may be contributing to the lack of decrease in the rate of stillbirth in the United States over the past decade.

Particularly devastating is the occurrence of a term stillbirth, a proportion of which has no clinical explanation or certain cause despite a complete evaluation. Huang et al[10] in their hospital-based cohort study of 84,294 births weighing 500 g or more from 1961 to 1974 and 1978 to 1996 found that two-thirds

For a list of participating institutions, see the Appendix online at http://links.lww.com/AOG/A202.

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of all unexplained fetal deaths occurred after 35 weeks of gestation. Experts have postulated that this outcome may be avoided by increased antenatal surveillance and intervening for risk factors such as advanced maternal age, although the evidence for this practice is limited.[11]

The purpose of this study was to identify possible risk factors for antepartum stillbirth and estimate their relative contribution stratified by parity in a large cohort of antepartum stillbirths with detailed medical record information controlling for a variety risk factors. In addition, this study attempted to determine whether potential demographic and prepregnancy factors can be used to identify women at a significantly higher risk for stillbirth at term compared with the general population.

MATERIALS AND METHODS

The Consortium on Safe Labor was a study conducted by the National Institute of Child Health and Human Development, National Institutes of Health, and has been described in detail elsewhere.[12] In brief, this was a retrospective cohort study involving 228,668 deliveries between 2002 and 2008 from 12 clinical centers and 19 hospitals representing nine American College of Obstetricians and Gynecologists districts. All deliveries at 23 weeks of gestation or greater were included in the Consortium on Safe Labor cohort. Women could have more than one pregnancy in the cohort; so to avoid intraperson correlation, we only included the first pregnancy enrolled for a total of 206,969 women. Two institutions that had a large percentage of components of the maternal medical history missing were excluded from these analyses. Institutional Review Board approval was obtained by all participating institutions.

Demographic data, medical history, prenatal, labor, and delivery information as well as postpartum and neonatal outcomes were extracted from electronic medical records from each institution. Data from the neonatal intensive care unit were collected and linked to the newborn record. Maternal and newborn discharge International Classification of Diseases, 9th Revision codes were also collected for each delivery. Data were transferred in electronic format from each site and were mapped to common categories for each predefined variable at the data coordinating center. Data inquiries, cleaning, and logic checking were performed. Validation studies were performed for four key variables and the electronic medical records were found to be a reasonably accurate representation of the medical charts.[12]

All singleton deliveries at 23 weeks of gestation or more from 10 institutions that have comprehensive electronic obstetric and neonatal databases were obtained and comprise the cohort for this analysis. Antepartum stillbirth included in this study was defined as a fetus having no signs of life before labor and Apgar scores of 0 and 0 at 1 minute and 5 minutes. Intrapartum stillbirth was defined as fetal death during labor. Live birth was defined as a newborn having a nonzero Apgar score at birth.

The primary outcome variable studied in the cohort was the occurrence of antepartum stillbirth compared with live birth at 23 weeks of gestation and beyond. Information on prepregnancy factors was abstracted from the institutions' electronic medical records. The following maternal characteristics were included: race (non-Hispanic white, non-Hispanic African American, Hispanic, Asian, other or multiracial), maternal age (younger than 20, 20–24, 25–29, 30–34, 35–39, 40 years or older), marital status (married, not married or unknown), insurance (private, public, self-pay, other or unknown), parity (nulliparous women, multiparous women); prior cesarean delivery, prior preterm birth, preexisting diabetes, chronic hypertension, smoking prior or during pregnancy, alcohol prior or during pregnancy, prepregnancy body mass index (BMI, calculated as weight (kg)/[height (m)]^2) (underweight [less than 18.5], normal weight [18.5–24.9], overweight [25–29.9], obese [30 or greater], and missing), and human immunodeficiency virus status. Because missing information may not occur at random, we treated missing values as a separate category.

Univariable analysis was performed using the chi square test. Multivariable analysis of the gestational age at stillbirth (with gestational age at live birth as a censoring time) used Cox proportional hazard regression to calculate adjusted hazard ratios and 95% confidence intervals (CIs) to assess the strength of the relationship between a potential risk factor and the occurrence of antepartum stillbirth. Subsequently, adjusted hazard ratios and 95% CIs were calculated stratified by parity. Our multivariable model was a generalized linear mixed model with site (center) as a random effect using PROC GLIMMIX in SAS.

To determine whether the prepregnancy risk factors for stillbirth were the same for stillbirths at term, we repeated the analysis in singleton pregnancies that delivered between 37 and 42 weeks of gestation using only race, maternal age, parity, BMI, preexisting diabetes, and chronic hypertension. As a result of a small number of women 40 years old or older with an antepartum stillbirth in the cohort

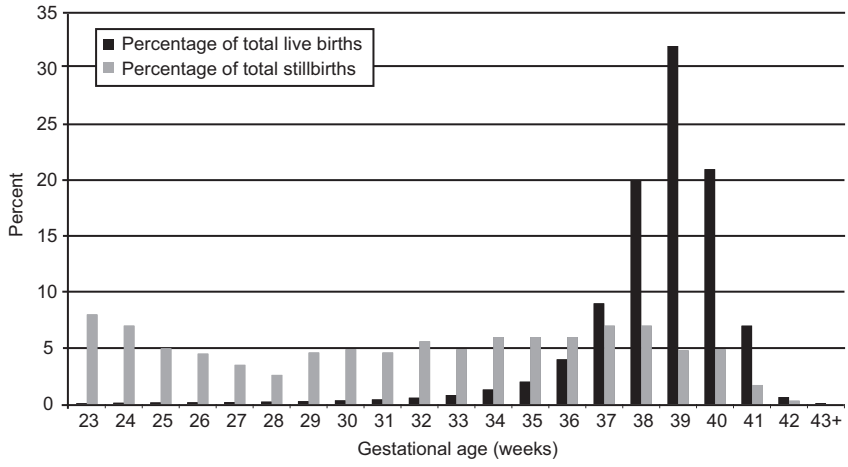

Fig. 1. The distribution of antepartum stillbirths and live births in the cohort by gestational age in weeks.
Reddy. Antepartum Stillbirth Risk Factors. Obstet Gynecol 2010.

(n=7), a single category of maternal age 35 years old or older was used. To calculate an absolute risk of stillbirth based on various individual and combined risk factors, we first computed a baseline absolute risk in women who served as the reference group in the Cox model (ie, non-Hispanic white, multiparous women, 25–29 years old, normal BMI [18.5–24.9], nondiabetic, and no history of chronic hypertension). Then we used the adjusted hazard ratios from the Cox model to calculate adjusted absolute risks for each individual risk factor. We also used the adjusted β-coefficients in the Cox model to calculate combined adjusted absolute risks for women who carried multiple risk factors.[13] Statistical analysis was performed using SAS 9.1.

RESULTS

The overall rate of stillbirth was 5.2 per 1,000 births at or after 23 weeks of gestation in the Consortium on Safe Labor cohort. There were a total 183,760 births at 23 weeks of gestation and beyond in this cohort of women delivering in 10 institutions. A total of 8,951 deliveries were excluded, which consisted of 8,076 multiple gestations, 109 intrapartum stillbirths, 78 not specified stillbirths, 574 neonatal deaths, and 272 women for missing maternal age (there was overlap among multiple gestation births, stillbirths, and births with maternal age missing), leaving 174,809 singleton deliveries to be analyzed. A total of 712 singleton antepartum stillbirths were compared with 174,097 singleton live births for prepregnancy risk factors. The average gestational age at delivery for antepartum singleton stillbirths was 31.9 weeks compared with 38.5 weeks for live births. Figure 1 shows the gestational age distribution for singleton antepartum stillbirths and singleton live births in this cohort.

Race, maternal age, marital status, insurance, parity, preexisting diabetes, chronic hypertension, smoking, alcohol, prepregnancy BMI 30 or greater, and human immunodeficiency virus were all significantly associated with antepartum stillbirth in univariable analyses (Table 1). When analyses were stratified by parity, race, maternal age, marital status, insurance, preexisting diabetes, chronic hypertension, and prepregnancy BMI 30 or greater were all significantly associated with antepartum stillbirth regardless of parity. For nulliparous women (parity 0), human immunodeficiency virus status was significantly associated with antepartum stillbirth. For multiparous women (parity 1 or greater), previous preterm birth, smoking, and alcohol were significantly associated with antepartum stillbirth. A history of cesarean delivery showed a trend with being associated with antepartum stillbirth but did not reach statistical significance (P=.06).

Multivariable analyses were performed in the entire cohort (N=174,809) and adjusted hazard ratios and 95% CIs were calculated (Table 2). African-American and Hispanic women had a 2.0- (95% CI 1.6–2.4) and 1.5-fold (95% CI 1.2–1.9) increased risk of antepartum stillbirth, respectively, when compared with white women. Asian race was associated with half of the antepartum stillbirth risk compared with white women (adjusted hazard ratio, 0.5; 95% CI 0.3–0.9). Maternal ages 35–39 years old and 40 years and older were associated with a 1.4-fold (95% CI 1.1–1.8) and 1.6-fold (95% CI 1.1–2.3) increased antepartum stillbirth risk compared with women 25–29 years old. Nulliparity was associated with a 1.2-fold (95% CI 1.1–1.5) increased risk of antepartum stillbirth. Preexisting diabetes (adjusted hazard ratio, 2.7; 95% CI 1.8–3.9), chronic hypertension (adjusted

Table 1. Univariable Analyses of Prepregnancy Characteristics Comparing Antepartum Singleton Stillbirths With Singleton Live Births Stratified by Parity

Maternal Characteristic	Whole Population			Nulliparous Women (Parity 0)			Multiparous Women (Parity Greater Than 1)		
	Singleton Live Birth (n=174,097)	Antepartum Singleton Stillbirth (n=712)	*P*	Singleton Live Birth (n=75,939)	Antepartum Singleton Stillbirth (n=346)	*P*	Singleton Live Birth (n=98,158)	Antepartum Singleton Stillbirth (n=366)	*P*
Race									
White, non-Hispanic	90,778 (52.1)	239 (33.6)	<.001	39,808 (52.4)	121 (35.0)	<.001	50,970 (51.9)	118 (32.2)	<.001
African American, non-Hispanic	33,737 (19.4)	226 (31.7)	—	14,294 (18.8)	113 (32.7)	—	19,443 (19.8)	113 (30.9)	—
Hispanic	29,271 (16.8)	141 (19.8)	—	11,789 (15.5)	62 (17.9)	—	17,482 (17.8)	79 (21.6)	—
Asian	7,250 (4.2)	10 (1.4)	—	3,817 (5.0)	4 (1.2)	—	3,433 (3.5)	6 (1.6)	—
Other, multiracial, or unknown	13,061 (7.5)	96 (13.5)	—	6,231 (8.2)	46 (13.3)	—	6,830 (7.0)	50 (13.7)	—
Maternal age (y)									
Younger than 20	15,126 (8.7)	84 (11.8)	<.001	13,040 (17.2)	75 (21.7)	.15	2,086 (2.1)	9 (2.5)	<.001
20–24	42,372 (24.3)	177 (24.9)	—	24,814 (32.7)	111 (32.1)	—	17,558 (17.9)	66 (18.0)	—
25–29	49,041 (28.2)	171 (24.0)	—	18,544 (24.4)	83 (24.0)	—	30,497 (31.1)	88 (24.0)	—
30–34	40,136 (23.1)	135 (19.0)	—	12,310 (16.2)	52 (15.0)	—	27,826 (28.3)	83 (22.7)	—
35–39	21,708 (12.5)	109 (15.3)	—	5,786 (7.6)	17 (4.9)	—	15,922 (16.2)	92 (25.1)	—
Older than 40	5,714 (3.3)	36 (5.1)	—	1,445 (1.9)	8 (2.3)	—	4,269 (4.3)	28 (7.7)	—
Marital									
Married	105,553 (60.6)	332 (46.6)	<.001	41,558 (54.7)	135 (39.0)	<.001	63,995 (65.2)	197 (53.8)	<.001
Not married or unknown	68,544 (39.4)	380 (53.4)	—	34,381 (45.3)	211 (61.0)	—	34,163 (34.8)	169 (46.2)	—
Insurance									
Private	102,225 (58.7)	321 (45.1)	<.001	44,477 (58.6)	149 (43.1)	<.001	57,748 (58.8)	172 (47.0)	<.001
Public	49,145 (28.2)	200 (28.1)	—	20,378 (26.8)	104 (30.1)	—	28,767 (29.3)	96 (26.2)	—
Self-pay	1,929 (1.1)	11 (1.5)	—	881 (1.2)	2 (0.6)	—	1,048 (1.1)	9 (2.5)	—
Other or unknown	20,798 (11.9)	180 (25.3)	—	10,203 (13.4)	91 (26.3)	—	10,595 (10.8)	89 (24.3)	—
Parity									
Nulliparous	75,939 (43.6)	346 (48.6)	.008	—	—	—	—	—	—
Multiparous	98,158 (56.4)	366 (51.4)	—	—	—	—	—	—	—
Prior cesarean delivery									
No or unknown	—	—	—	—	—	—	75,960 (77.4)	268 (73.2)	.06
Yes	—	—	—	—	—	—	22,198 (22.6)	98 (26.8)	—
Preterm birth									
No or unknown	—	—	—	—	—	—	87,175 (88.8)	310 (84.7)	.01
Yes	—	—	—	—	—	—	10,983 (11.2)	56 (15.3)	—
Preexisting diabetes									
No or unknown	171,494 (98.5)	682 (95.8)	<.001	74,981 (98.7)	332 (96.0)	<.001	96,513 (98.3)	350 (95.6)	<.001
Yes	2,603 (1.5)	30 (4.2)	—	958 (1.3)	14 (4.0)	—	1,645 (1.7)	16 (4.4)	—
Chronic hypertension									
No or unknown	155,832 (89.5)	612 (86.0)	<.001	68,492 (90.2)	300 (86.7)	<.001	87,340 (89.0)	312 (85.2)	<.001
Yes	4,463 (2.6)	47 (6.6)	—	1,855 (2.4)	21 (6.1)	—	2,608 (2.7)	26 (7.1)	—
Missing	13,802 (7.9)	53 (7.4)	—	5,592 (7.4)	25 (7.2)	—	8,210 (8.3)	28 (7.7)	—
Smoking prior to or during pregnancy									
No or unknown	163,120 (93.7)	644 (90.4)	<.001	71,922 (94.7)	320 (92.5)	.07	91,198 (92.9)	324 (88.5)	.001
Yes	10,977 (6.3)	68 (9.6)	—	4,017 (5.3)	26 (7.5)	—	6,960 (7.1)	42 (11.5)	—
Alcohol prior to or during pregnancy									
No or unknown	170,965 (98.2)	690 (96.9)	.01	74,559 (98.2)	339 (98.0)	.77	96,406 (98.2)	351 (95.9)	<.001
Yes	3,132 (1.8)	22 (3.1)	—	1,380 (1.8)	7 (2.0)	—	1,752 (1.8)	15 (4.1)	—
Prepregnancy BMI (kg/m^2)									
Missing	55,199 (31.7)	262 (36.8)	<.001	24,107 (31.7)	137 (39.6)	.01	31,092 (31.7)	125 (34.2)	.01
Underweight (less than 18.5)	6,508 (3.7)	19 (2.7)	—	3,494 (4.6)	12 (3.5)	—	3,014 (3.1)	7 (1.9)	—
Normal weight (18.5–25)	64,617 (37.1)	220 (30.9)	—	30,992 (40.8)	117 (33.8)	—	33,625 (34.3)	103 (28.1)	—
Overweight (25–30)	26,489 (15.2)	103 (14.5)	—	10,238 (13.5)	43 (12.4)	—	16,251 (16.6)	60 (16.4)	—
30 or higher	21,284 (12.2)	108 (15.2)	—	7,108 (9.4)	37 (10.7)	—	14,176 (14.4)	71 (19.4)	—
HIV or AIDS									
No or unknown	166,315 (95.5)	676 (94.9)	.02	72,687 (95.7)	331 (95.7)	.02	93,628 (95.4)	345 (94.3)	.23
Yes	731 (0.4)	8 (1.1)	—	244 (0.3)	4 (1.2)	—	487 (0.5)	4 (1.1)	—
Missing	7,051 (4.1)	28 (3.9)	—	3,008 (4.0)	11 (3.2)	—	4,043 (4.1)	17 (4.6)	—

BMI, body mass index; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.
Data are frequency (%) unless otherwise specified.

Table 2. Multivariable Analyses of Prepregnancy Characteristics Comparing Antepartum Singleton Stillbirths With Singleton Live Births Stratified by Parity

	Whole Population (N=174,809)	Nulliparous Women (n=76,285)	Multiparous Women (n= 98,524)
Race			
White, non-Hispanic	Referent	Referent	Referent
African American, non-Hispanic	2.0 (1.6–2.4)	1.9 (1.4–2.6)	1.9 (1.4–2.6)
Hispanic	1.5 (1.2–1.9)	1.3 (0.9–1.8)	1.7 (1.2–2.3)
Asian	0.5 (0.3–0.9)	0.3 (0.1–0.9)	0.7 (0.3–1.6)
Other, multiracial, or unknown	2.4 (1.8–3.0)	2.0 (1.4–2.8)	2.8 (2.0–4.0)
Maternal age (y)			
25–29	Referent	Referent	Referent
Younger than 20	1.1 (0.8–1.4)	0.9 (0.6–1.2)	1.2 (0.6–2.5)
20–24	1.0 (0.8–1.3)	0.9 (0.6–1.2)	1.2 (0.9–1.6)
30–34	1.0 (0.8–1.2)	0.9 (0.6–1.3)	1.0 (0.8–1.4)
35–39	1.4 (1.1–1.8)	0.6 (0.4–1.0)	1.9 (1.4–2.5)
Older than 40	1.6 (1.1–2.3)	1.0 (0.5–2.2)	2.0 (1.3–3.0)
Marital status			
Married	Referent	Referent	Referent
Not married or unknown	1.2 (1.0–1.5)	1.3 (1.0–1.7)	1.1 (0.9–1.5)
Insurance			
Private	Referent	Referent	Referent
Public	0.9 (0.8–1.1)	1.1 (0.8–1.5)	0.8 (0.6–1.0)
Self-pay	1.3 (0.7–2.3)	0.5 (0.1–2.0)	1.9 (1.0–3.8)
Other or unknown	2.4 (2.0–3.0)	2.8 (2.1–3.7)	2.3 (1.7–3.1)
Parity			
Multiparous	Referent		
Nulliparous	1.2 (1.1–1.5)		
Prior cesarean delivery			
No or unknown			Referent
Yes			1.3 (1.0–1.6)
Preterm birth			
No or unknown			Referent
Yes			1.6 (1.2–2.1)
Preexisting diabetes			
No or unknown	Referent	Referent	Referent
Yes	2.7 (1.8–3.9)	3.5 (2.0–6.1)	2.1 (1.3–3.5)
Chronic hypertension			
No or unknown	Referent	Referent	Referent
Yes	2.0 (1.5–2.8)	2.1 (1.3–3.3)	1.9 (1.3–3.0)
Missing	1.1 (0.8–1.5)	1.1 (0.7–1.6)	1.2 (0.8–1.8)
Smoking during pregnancy			
No or unknown	Referent	Referent	Referent
Yes	1.6 (1.2–2.1)	1.5 (1.0–2.2)	1.7 (1.2–2.3)
Alcohol during pregnancy			
No or unknown	Referent	Referent	Referent
Yes	1.7 (1.1–2.6)	1.1 (0.5–2.4)	2.2 (1.3–3.8)
Prepregnancy BMI (kg/m^2)			
Normal weight (18.5–25)	Referent	Referent	Referent
Missing	1.5 (1.2–1.8)	1.7 (1.3–2.3)	1.3 (1.0–1.7)
Underweight (less than 18.5)	0.9 (0.5–1.4)	0.9 (0.5–1.6)	0.8 (0.4–1.8)
Overweight (25–30)	1.1 (0.8–1.4)	1.0 (0.7–1.5)	1.1 (0.8–1.5)
30 or higher	1.3 (1.0–1.7)	1.2 (0.8–1.7)	1.4 (1.0–1.9)
HIV or AIDS			
No or unknown	Referent	Referent	Referent
Yes	1.9 (0.9–3.8)	2.5 (0.9–6.7)	1.5 (0.6–4.0)
Missing	1.2 (0.8–1.8)	0.9 (0.5–1.6)	1.5 (0.9–2.5)

BMI, body mass index; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.
Data are adjusted hazard ratio (95% confidence interval).

hazard ratio, 2.0; 95% CI 1.5–2.8), smoking (adjusted hazard ratio, 1.6; 95% CI 1.2–2.1), and alcohol use (adjusted hazard ratio, 1.7; 95% CI 1.1–2.6) were all independently associated with antepartum stillbirth when compared with women without these conditions. Prepregnancy BMI 30 or greater was associated with a 1.3-fold (95% CI 1.0–1.7) increased risk of antepartum stillbirth compared with normal weight women (BMI, 18.5–24.9).

Because multiparous women have different risk factors for stillbirth that nulliparous women are not at risk for, multivariable analyses were then performed stratified by parity (Table 2). In nulliparous women (n=76,285), African-American race, preexisting diabetes, chronic hypertension, and smoking were associated with antepartum stillbirth when adjusted for the other risk factors. Analyses of the multiparous women cohort (n=98,524) demonstrated two additional risk factors associated with an increased antepartum stillbirth risk. The risk of antepartum stillbirth increased 1.3-fold (95% CI 1.0–1.6) for a history of cesarean delivery and 1.6-fold (95% CI 1.2–2.1) for history of preterm birth when adjusted for the other risk factors. There was an increased antepartum stillbirth risk associated with African-American and Hispanic race, maternal age 35 years or older, preexisting diabetes, chronic hypertension, smoking, alcohol, and prepregnancy BMI greater than 30 in multiparous women when adjusted for the other risk factors.

To determine whether the prepregnancy risk factors for stillbirth were the same for stillbirths at term, we repeated the analysis in 155,859 singleton pregnancies that delivered between 37 and 42 weeks of gestation, which was comprised of 155,544 singleton live births and 185 singleton antepartum stillbirths. For women who delivered between 37 and 42 weeks of gestation who were in the referent group for all six variables (non-Hispanic white, 25–29 years old, normal weight [BMI 18.5–25], multiparous, no chronic hypertension, and no preexisting diabetes), the baseline risk of stillbirth at 37–42 weeks of gestation was exceedingly low: 0.8 per 1,000. The adjusted absolute risk of stillbirth in ongoing pregnancies at 37 weeks of gestation increased as the following factors were changed individually (leaving the other variables in the referent group): preexisting diabetes (3.1 per 1,000), chronic hypertension (1.7 per 1,000), African-American race (1.8 per 1,000), maternal age 35 years old or older (1.3 per 1,000), BMI greater than 30 (1 per 1,000), and nulliparity (0.9 per 1,000). Women who were African American, 35 years old or older, nulliparous, and BMI 30 or greater without diabetes or chronic hypertension had an absolute risk of stillbirth of 4.4 per 1,000 of ongoing pregnancies (a relative risk of 5.5 compared with women with no risk factors [the referent group]).

DISCUSSION

This study represents a large cohort of viable pregnancies (23 weeks of gestation and greater) to study the risk of antepartum stillbirth in the United States with detailed information from electronic medical records. Like in previous studies, the following factors were associated with increased risk of antepartum stillbirth: African-American race, Hispanic race, nulliparity, advanced maternal age (older than 35 years old), prepregnancy BMI greater than 30, smoking, chronic hypertension, and prepregnancy diabetes.[3–6,9] Because of the large number of women in the cohort, adjusted hazard ratios could be calculated controlling for all these variables, which is unique and confirms the individual contribution of each risk factor to antepartum stillbirth.

Smoking, alcohol consumption, and obesity were demonstrated to be independent risk factors even when adjusting for other relevant variables such as preexisting diabetes, hypertension, maternal age, and race. Because these are modifiable risk factors for stillbirth, preconception care should be directed at smoking and drinking cessation and optimizing prepregnancy weight. Women who quit smoking from their first to second pregnancy have been shown to reduce their risk of stillbirth to the same level as nonsmokers in the second pregnancy.[14]

Previous preterm birth was a significant risk factor for stillbirth with a 1.6-fold increased risk of stillbirth. The relationship with previous preterm birth has been reported in other studies.[2] In clinical practice, the focus for women with a previous preterm birth has been to prevent recurrent preterm birth. Even controlling for covariates such as pregestational maternal disease and exposures that are associated with preterm birth and stillbirth, a consistent relationship between previous preterm birth and stillbirth is seen in this study. This reinforces the concept that preterm birth in a prior pregnancy is a marker for biologic susceptibility to adverse pregnancy outcome beyond recurrent preterm birth.

Previous cesarean delivery was independently associated with a 1.3-fold increased risk of antepartum stillbirth in our study. The relationship between previous cesarean delivery and subsequent antepartum stillbirth has been controversial. A large study of more than 100,000 births in Scotland reported a 1.6-fold increased risk of unexplained stillbirth (95% CI 1.2–2.3) in women with a previous cesarean

delivery.[15] An analysis of birth certificate data from almost 400,000 births in Missouri demonstrated a 1.4-fold increased risk of stillbirth (95% CI 1.1–1.7) with previous cesarean delivery for African-American women but no association among white women.[16] However, an analysis of U.S. birth certificate and fetal death report data between 1995 and 1997 of more than 11 million records showed no association between previous caesarean delivery and the risk of stillbirth.[17] Vital statistics data have certain limitations. First, misclassification of history of previous cesarean delivery may occur using birth certificate data with repeat cesarean delivery with labor and vaginal birth after cesarean delivery being known to be significantly underreported.[18] Also, because U.S. fetal death data are collected on a separate data-collection form from live births or infant deaths, fetal death data may have more data-quality issues and a higher percentage of nonstated responses for certain variables such as method of delivery than do either live birth or infant death data.[19] Our data confirm a 1.3-fold increase risk of antepartum stillbirth for women with a previous cesarean delivery controlling for important covariates such as maternal disease, race, prior preterm delivery, and BMI. As the overall rates of cesarean delivery continue to increase in the United States, an association between cesarean delivery and subsequent stillbirth risk is concerning.

Despite analyzing a large cohort of pregnancies with detailed electronic medical records, there are limitations to the study. A limitation was the inability to analyze the data according to likely cause of death. Unlike live births in which congenital anomalies, neonatal morbidities, and cause of death are captured in the neonatal charts, the results of perinatal autopsy and the stillbirth workup are not captured in the maternal chart and a separate chart of the stillbirth similar to a neonatal chart was not generated. This fact makes research on stillbirth difficult and requires prospective collection of this information. In addition, despite using medical records, conditions such as assisted reproductive technology and previous stillbirth could not be analyzed as a result of a high percentage of missing data. However, when considering our analyses of term stillbirths, these limitations of the data are less of an issue because the majority are unexplained.[10] They are not associated with preterm premature rupture of fetal membranes and less likely to be associated with karyotypic abnormalities and congenital anomalies. We were also unable to analyze the use of antepartum testing in the cohort. Presumably women with conditions such as pregestational diabetes and chronic hypertension underwent antepartum testing, which may have decreased the stillbirth risk observed with these conditions in this study. Likewise, although there is no American College of Obstetricians and Gynecologists recommendation regarding testing for factors such as advanced maternal age or obesity for example, the performance of antepartum testing may have decreased the stillbirth risk associated with these factors in this cohort. Lastly, although there was wide geographic variation among the participating centers, this cohort may not be representative of the United States because some of these hospitals are tertiary care centers; women delivering at these centers may differ in certain characteristics influencing pregnancy outcome. In a population without preexisting medical disease or other obstetric complications, there are few direct data to assess whether antepartum testing will improve fetal outcomes.

We focused on term stillbirths because the institution of antepartum testing for the presence of risk factors is not without consequence. Antepartum testing is associated with false-positive results, which may lead to further unnecessary testing or delivery. In the case of preterm gestations, antepartum testing to prevent stillbirth could lead to iatrogenic preterm delivery, which would be undesirable.

Advanced maternal age by itself has been identified as a significant risk factor for stillbirth at term and the benefits and risks of routine antepartum testing on the basis of maternal age alone has been explored.[20] Fretts et al[11] studied both maternal age and parity as predictors of unexplained fetal death in the McGill Obstetrical Neonatal Database data set. The authors found that nulliparous women aged 35 years and older had a 3.3-fold increase in the risk of unexplained fetal death compared with women younger than 35 years of age. The odds ratio for maternal age 40 years and older was 3.7. Their conclusion was that compared with no testing, a policy of weekly antepartum testing beginning at 37 weeks of gestation in otherwise low-risk women aged 35 years and older, with induction of labor for women with abnormal test results, would result in a reduction in unexplained fetal deaths.

In our study, the absolute risk of stillbirth in women with maternal age older than 35 years old (1.3 per 1,000) was lower than in the Fretts et al study. The lower rate in our study is likely because we were able to control for a large number of covariates as a result of the large number of antepartum stillbirths in our cohort. Thus, maternal age older than 35 years by itself was associated with a relatively low risk of stillbirth. This low risk may not apply to women older

than 40 years old because of the small number of women older than 40 years old reaching term in our cohort. Only when maternal age was combined with other risk factors such as African-American race and BMI greater than 30 mg/m^2 did the risk of stillbirth approach a level similar to that of a woman with prepregnancy diabetes or chronic hypertension. In addition, there is no evidence that by performing antepartum fetal testing the occurrence of stillbirth will be averted because the mechanism associated with advanced maternal age is unknown and may be unrelated to the detection of placental insufficiency.

The ability of individual risk factors of race, parity, advanced maternal age (35–39 years old) and BMI to predict term stillbirth is poor, and this holds true even when these factors are combined. Our results do not support routine antenatal surveillance at term for any of these risk factors when present in isolation. Among multiparous women, previous preterm birth and previous cesarean delivery are risk factors for antepartum stillbirth. If a risk scoring system can be developed to identify women at the highest risk for stillbirth, interventions such as antepartum fetal surveillance with earlier delivery if indicated may be performed to prevent the occurrence of this devastating outcome.

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