Racial/ethnic disparity in severe maternal morbidity among women who conceived by in vitro fertilization

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BACKGROUND: In vitro fertilization (IVF) as a fertility treatment is associated with adverse perinatal outcomes. Racial/ethnic disparity in severe maternal morbidity (SMM) in women who conceived by IVF is understudied.

OBJECTIVE: To examine differences in the association between race/ethnicity and SMM between women who conceived spontaneously and those who conceived using IVF.

METHODS: We included all singleton live births and stillbirths in the United States, 2016–2021; data were obtained from the National Center for Health Statistics. Maternal race/ethnicity included non-Hispanic White (NHW), non-Hispanic Black (NHB), American Indian and Alaska Native (AIAN), Asian, Pacific Islander (PI), Hispanic, and mixed-race categories. The SMM composite outcome included eclampsia, uterine rupture, peripartum hysterectomy, blood transfusion, and intensive care unit (ICU) admission. We used logistic regression to adjust for potential confounders (such as age, education, parity, prepregnancy body mass index, smoking during pregnancy, chronic hypertension, and preexisting diabetes) and to assess modification of the association between race/ethnicity and SMM by IVF.

RESULTS: The study population included 21,585,015 women: 52% were NHW, 15% NHB, 0.8% AIAN, 6% Asian, 0.2% PI, 24% Hispanic, and 2% were of mixed race. IVF was used by 183,662 (0.85%) women; the rate of the SMM composite outcome was 18.5 per 1000 deliveries and 7.9 per 1000 deliveries in the IVF and spontaneous conception groups, respectively (unadjusted rate ratio 2.34, 95% confidence interval [CI] 2.26–2.43). In women with spontaneous conception, NHB, Asian and mixed-race women had elevated odds of SMM compared with NHW women (adjusted odds ratio [aOR]=1.39, 95% CI 1.37–1.41; aOR=1.04, 95% CI 1.02–1.07; and aOR=1.42, 95% CI 1.38–1.46, respectively). Racial/ethnic disparities in SMM and its components were not different between the IVF and spontaneous conception groups for the mixed-race category. NHB and Hispanic women had significantly higher aORs for uterine rupture/intrapartum hysterectomy compared with NHW women in the IVF group, while Asian women had a higher aOR for ICU admission compared with NHW women in the IVF group.

CONCLUSION: Women who conceived by IVF have a greater than two-fold higher risk of SMM and this higher risk is evident across all racial/ethnic groups. However, NHB and Hispanic women who conceived by IVF had a higher risk of uterine rupture/hysterectomy, and Asian women who conceived by IVF had a higher risk of ICU admission. Our results warrant further investigation examining pregnancy and postpartum care issues among racial/ethnic minority women who conceive using IVF.

Key words: IVF, severe maternal morbidity, racial/ethnic disparity

Introduction

Global fertility rates have declined in recent decades, with a correlated decline in live birth rates.[1,2] Infertility, defined as the failure to conceive after 12 months of regular unprotected sexual intercourse, is becoming increasingly prevalent globally.[3,4] For instance, in the United States (US), approximately

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Why was this study conducted?

- Racial/ethnic disparities in severe maternal morbidity (SMM) are well documented.
- We examined whether these disparities are less pronounced in women with singleton pregnancies who used in vitro fertilization (IVF) to conceive.

Key findings

- Among women with IVF conception, racial/ethnic disparities are larger for some SMM components compared with women who conceived spontaneously; for example, adjusted odds ratios for uterine rupture/intrapartum hysterectomy in Hispanic and non-Hispanic Black women vs non-Hispanic White women are higher in IVF-conceived than in spontaneous pregnancies.
- The association between IVF and SMM is stronger than the association between race/ethnicity and SMM.

What does this add to what is known?

- Racial/ethnic disparity is larger for some SMM components in women with singleton pregnancies who conceived using IVF vs those with spontaneous conception.

8.5% of women of reproductive age were diagnosed with infertility in 2015−2019.[5] Increased age at first pregnancy, greater exposure to pollutants, and sexually transmitted infections are contributing factors.[4,6,7] Recent studies also show a reduced sperm count in males and lower oocyte quality in females,[4,8] and an increasing number of couples are using assisted reproductive technologies (ART) to conceive.[9]

The Centers for Disease Control and Prevention (CDC) in the US defines ART as "all fertility treatments in which either eggs or embryos are handled."[10] Over 99% of all ART treatments involve in vitro fertilization (IVF), which is frequently combined with intracytoplasmic sperm injection.[11] IVF is a risk factor for adverse maternal outcomes, (such as gestational diabetes, gestational hypertension, and severe maternal morbidity, [SMM] eg, eclampsia), and fetal/infant adverse outcomes (such as congenital anomalies, preterm birth, and perinatal death).[12−16]

Racial/ethnic disparities in reproductive health and adverse pregnancy outcomes have been well documented in the US.[17−22] For example, non-Hispanic Black (NHB) women are two to three times more likely to die or suffer severe morbidity from pregnancy-related conditions, while American Indian/Alaskan Native women are more likely to deliver via cesarean section than non-Hispanic White (NHW) women.[17−19] Although these disparities reflect differences in socioeconomic status (SES) and healthcare access for various racial and ethnic groups in the US, individual risk factors and SES do not completely explain these disparities.[20−22]

Few studies have examined the effects of race and ethnicity on perinatal outcomes of women who conceived by IVF. One study showed that racial/ethnic disparities in adverse fetal and infant outcomes are larger in women who conceived by IVF than in those conceived spontaneously.[23] For instance, the disparity in neonatal mortality between NHB and NHW women was two-fold larger in those who conceived by IVF compared with the disparity in women who conceived spontaneously.[23] Although this finding of a larger IVF-related perinatal death disparity by race/ethnicity may have been, in part, due to underlying disparities in rates of SMM, racial/ethnic disparities in SMM in women who used IVF to conceive have not been adequately studied. We, therefore, carried out a population-based study examining the effects of IVF on several SMM conditions and racial/ethnic disparities in these conditions among women who conceived by IVF.

Methods

Data sources and study population

The study population included all women who delivered a singleton live birth or stillbirth in the US from 2016 to 2021. We used National Center for Health Statistics (NCHS) data that included information from live birth and fetal death certificates.[24,25] These files comprise self-reported and chart-abstracted data on demographic and clinical characteristics, pregnancy complications, and birth outcomes for all live births and stillbirths in the US. We excluded births occurring before 20 weeks and after 44 weeks gestation and those with missing data on gestational age, plurality, race, and ethnicity, or mode of conception. Live birth and fetal death certificates included self-reported information about assisted reproduction, either IVF or other treatments. For the group of women identified as having delivered following use of ART, we included women who indicated that they used "assisted reproductive technology (eg, IVF, gamete intrafallopian transfer)."[24,25] Women who conceived using other modes of assisted conception (eg, fertility drug treatment or artificial insemination) were excluded, while all other women constituted the comparison group who conceived spontaneously. The datasets were publicly accessible and deidentified, thus the study did not require ethics approval. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc).

SMM and race/ethnicity

SMM is defined by the CDC as "unexpected outcomes of labor and delivery that can result in significant short- or long-term health consequences."[16] We used NCHS national-level data that include information on five SMM conditions, which were the primary outcomes of interest in this study. These included eclampsia, blood transfusion, uterine rupture, intrapartum hysterectomy, and intensive care unit (ICU) admission. Uterine rupture and intrapartum hysterectomy are very rare and often concurrent events, and therefore we combined these two morbidities into

one category. Although ICU admission is not a medical condition per se, this was denoted as severe morbidity since women admitted to ICU are very likely to have or have had a serious complication requiring close monitoring and care. Besides the 4 severe morbidity conditions listed above we also examined composite SMM which included any of these conditions (eclampsia, blood transfusion, uterine rupture/intrapartum hysterectomy, and ICU admission).

The categories of self-reported maternal race and ethnicity were based on NCHS categories[26] and included: (1) NHW, (2) NHB; (3) American Indian and Alaska Native (AIAN); (4) Asian (Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, and other Asian); (5) Pacific Islander (PI) (Native Hawaiian, Guamanian or Chamorro, Samoan, and Other PI); (6) Hispanic (all women of Hispanic origin: Mexican, Mexican American, Chicana, Puerto Rican, Cuban, and other Hispanic origin, regardless of race) and (7) mixed/other race. The mixed-race category comprised women whose race/ethnicity could not be described by any one of the previously mentioned categories.

Statistical analysis

The primary independent variable was race/ethnicity, and IVF was examined as a factor that potentially modified the effect of race/ethnicity on SMM. We quantified rates of SMM outcomes, and compared SMM rates between women with IVF vs spontaneous conception within categories of race/ethnicity. Rate ratios (RR) and rate differences (RD) with 95% confidence intervals (CI) were used to express differences in SMM rates.

We used logistic regression models to quantify the association between race/ethnicity and SMM (among women who did and did not use IVF) using adjusted odds ratios (aOR). The statistical significance of race/ethnicity differences in SMM frequency between IVF and spontaneous conception groups was assessed using interaction terms (between race/ethnicity and IVF) in the model. AORs were adjusted for maternal characteristics, including previous cesarean delivery, chronic hypertension, chronic diabetes, previous fetal death or termination of pregnancy, previous infant death, prepregnancy body mass index (BMI), maternal age (<25 and ≥35 years vs 25−34 years), parity (nulliparous, parity 1−3, parity ≥4), education (high school or higher vs less than high school), prenatal care (no prenatal care vs some prenatal care), smoking during pregnancy, and fetal sex (male vs female). BMI (kg/m^2) was categorized as follows: underweight (<18.5), normal BMI (18.5−24.9), overweight (25.0−29.9), and obesity class 1 (30.0−34.9), class 2 (35.0−39.9), and class 3 (≥40). These factors were selected for adjustment based on the previous literature and availability of the information in our data sources and used in a full model to address potential confounding. Records with missing values for any covariate (<3% in total) were excluded from multivariable analyses. We were not be able to adjust for the type of health care insurance (Medicaid, self-paid, and other vs private) in the primary analysis, because this information was not available for pregnancies ending in stillbirth (fetal death certificates). Therefore, sensitivity analyses restricted to live births were carried out, adjusting for the type of health care insurance.

Results

Study population

Overall, 21,990,215 women had a singleton live birth or stillbirth (at 20−44 weeks gestation) between 2016 and 2021. Our study population comprised 21,585,015 women, of whom 11,154,848 (52%) were NHW; 3145,738 (15%) were NHB; 167,468 (0.8%) were AIAN; 1367,352 (6%) were Asian; 55,930 (0.2%) were PI; 5210,196 (24%) were Hispanic; and 5210,196 (2%) were mixed-race. IVF was used by 183,662 (0.85%) of the study population. The proportion of women who used IVF by race/ethnicity was as follows: 127,982 (1.2%) of NHW women, 9535 (0.3%) of NHB women, 228 (0.1%) of AIAN women, 26,383 (1.9%) of Asian women, 104 (0.2%) of PI women, 16,224 (0.3%) of Hispanic women, and 3206 (0.7%) of mixed-race women. The differences in these proportions were statistically significant (P<.001; Supplementary Table 1).

Among women who conceived by IVF, more than 50% were above 35 years old, in each race/ethnicity category, while a majority (58%) of women who conceived spontaneously were between 25 and 34 years old. Women who used IVF were also more likely to be nulliparous, have secondary or higher education (>93% in each race/ethnic group), chronic diabetes and chronic hypertension, and more likely to deliver by cesarean section in the current pregnancy than women who conceived spontaneously. Rates of smoking and prepregnancy underweight were higher among women who conceived spontaneously (Supplementary Table 2).

Racial/ethnic disparities in risk factors for adverse pregnancy outcomes were generally similar between IVF and spontaneous conception groups, with the exception of PI women who had the highest proportion of obesity in the spontaneous conception group, and one of the lowest proportions of obesity in the IVF group (Table 1). Racial/ethnic disparities in other risk factors for SMM followed a similar pattern in IVF and spontaneous conception groups. For instance, Asian women had the highest proportion of nulliparous and older (≥35 years) women; NHW women had the highest proportion of women with secondary or higher education; NHB had the highest proportion of women with chronic hypertension; and AIAN mothers had the highest proportion of those who smoked in both groups. PI women had the highest proportion of women with preexisting diabetes in the IVF group but not among those with spontaneous conception (Table 1).

SMM by race/ethnicity and IVF

The rate of composite SMM was 18.5 per 1000 deliveries in the IVF group relative to 7.9 per 1000 deliveries in the group who conceived spontaneously (RR 2.34; 95% CI 2.26−2.43; RD 10.6 per 1000 deliveries, 95% CI 9.96−11.2 per 1000). The most frequent SMM

TABLE 1
Characteristics of women by race/ethnicity and mode of conception, singleton deliveries, United States, 2016–2021

	Spontaneous conception							IVF						
Clinical characteristics	NHW *N*=11,026,866 %	NHB *N*=313,6203 %	AIAN *N*=167,240 %	Asian *N*=1340,969 %	PI *N*=55,826 %	Hispanic *N*=5193,972 %	Mixed race *N*=480,277 %	NHW *N*=127,982 %	NHB *N*=9535 %	AIAN *N*=228 %	Asian *N*=26,383 %	PI *N*=104 %	Hispanic *N*=16,224 %	Mixed race *N*=3206 %
Maternal age (y)														
<25	20.5	32.4	37.0	6.9	30.8	31.4	34.8	0.7	1.3	2.6	0.3	1.0	1.5	1.4
25–34	61.6	52.5	51.1	64.7	54.1	52.3	51.5	42.4	33.5	37.7	33.2	40.4	36.8	37.4
≥35	17.9	15.2	11.9	28.5	15.1	16.4	13.7	56.9	65.2	59.7	66.5	58.7	61.7	61.2
Nullipara	39.7	36.0	30.9	45.2	29.8	34.9	41.9	58.3	63.9	51.3	64.8	59.6	59.7	60.4
BMI (kg/m^2)														
<18.5	3.1	2.9	2.1	6.6	1.5	2.3	3.3	2.0	0.9	0.9	4.4	1.0	1.5	2.0
18.5–24.9	44.7	30.9	29.4	58.5	22.3	34.4	39.0	49.9	25.9	35.1	59.5	43.3	38.6	47.2
25.0–29.9	24.9	25.9	26.6	22.8	24.7	29.8	25.3	24.9	33.2	26.8	24.0	30.8	30.4	26.3
≥30.0	25.5	37.1	39.3	9.7	45.5	30.9	30.3	21.8	37.8	36.8	10.4	23.1	27.9	23.3
Maternal education														
≤Primary	7.1	12.9	20.7	6.4	21.9	25.8	11.8	0.4	1.4	1.3	1.2	1.0	5.1	0.9
≥Secondary	92.3	86.1	78.5	92.1	76.1	72.8	87.6	98.9	97.3	97.8	97.4	95.2	93.2	98.3
Prior cesarean delivery														
No	85.7	82.6	84.4	84.8	82.4	83.2	86.2	84.8	84.5	79.4	86.8	87.5	86.6	84.6
1–2 deliveries	13.3	15.5	13.1	14.8	14.9	15.1	12.4	14.7	14.8	19.3	13.0	11.5	14.4	12.9
3+ deliveries	1.01	1.92	2.54	0.41	2.63	1.66	1.34	0.49	0.67	1.32	0.19	0.96	1.02	0.56
Chronic hypertension	2.0	4.2	2.9	1.1	1.9	1.4	2.4	3.3	8.8	6.1	2.6	6.7	3.3	4.4
Preexisting diabetes	0.8	1.3	2.5	1.0	2.0	1.1	1.0	0.9	2.1	2.6	1.7	3.9	1.6	1.2
Smoking in pregnancy	9.2	5.0	14.8	0.5	3.8	1.6	10.5	0.4	0.5	0.9	0.1	1.0	0.3	0.5
Cesarean delivery in current pregnancy	29.0	34.3	27.6	31.1	30.1	30.2	28.3	46.5	60.9	54.0	50.6	44.2	52.3	47.5
Gestational age (wk)														
20–33	1.9	4.6	2.9	1.9	3.2	2.4	2.5	3.2	8.9	4.8	4.3	4.8	5.4	4.3
34–36	5.6	8.1	7.8	5.5	7.7	6.4	6.5	8.0	11.2	10.5	7.8	14.4	9.5	7.6
≥37	92.5	87.4	89.3	92.6	89.1	91.3	91.1	88.8	80.0	84.7	87.9	80.8	85.0	88.1
Male fetal sex	51.3	50.8	51.0	51.6	51.5	51.0	51.1	50.9	50.8	51.8	52.7	47.1	50.5	51.7

Some percentages do not add up because of missing values; missing values <3% are not shown.

AIAN, American Indian and Alaska Native; *BMI*, Body Mass Index; *IVF*, in vitro fertilization; *NHB*, non-Hispanic Black; *NHW*, non-Hispanic White; *PI*, Pacific Islander.

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TABLE 2
Rates of severe maternal morbidity by race/ethnicity and mode of conception, singleton deliveries, United States, 2016–2021

			Composite SMM		ICU admission		Transfusion[b]		Eclampsia		Uterine rupture/ hysterectomy	
Conception mode	Race/ethnicity	Total *N*	*N*	Per 1000	*N*	Per 1000[a]	*N*	Per 1000[a]	*N*	Per 1000[a]	*N*	Per 1000[a]
Spontaneous	Non-Hispanic White	11,026,866	78,958	7.2	15,321	1.4	38,240	3.5	26,264	2.4	7690	0.7
	Non-Hispanic Black	3136,203	33,522	10.7	8115	2.6	14,478	4.6	11,225	3.6	2992	1.0
	AIAN	167,240	2863	17.1	413	2.5	1784	10.7	742	4.4	200	1.2
	Asian	1340,969	9464	7.1	2450	1.8	4287	3.2	3043	2.3	1082	0.8
	Pacific Islander	55,826	1313	23.5	176	3.2	365	6.5	794	14.2	70	1.3
	Hispanic	5193,972	37,594	7.2	8187	1.6	19,146	3.7	10,997	2.1	3603	0.7
	Mixed Race	480,277	5035	10.5	799	1.7	1787	3.7	2512	5.2	328	0.7
	All race/ethnicity	**21,401,353**	**168,749**	**7.9**	**35,461**	**1.7**	**80,087**	**3.7**	**55,577**	**2.6**	**15,965**	**0.7**
IVF	Non-Hispanic White	127,982	2292	17.9	434	3.4	1524	11.9	436	3.4	262	2.0
	Non-Hispanic Black	9535	250	26.2	68	7.1	156	16.4	47	4.9	39	4.1
	AIAN	228	5	21.9	0	0.0	3	13.2	1	4.4	1	4.4
	Asian	26,383	477	18.1	151	5.7	298	11.3	76	2.9	67	2.5
	Pacific Islander	104	2	19.2	1	9.6	2	19.2	0	0.0	0	0.0
	Hispanic	16,224	284	17.5	68	4.2	179	11.0	55	3.4	49	3.0
	Mixed Race	3206	82	25.6	18	5.6	49	15.3	21	6.6	5	1.6
	All race/ethnicity	**183,662**	**3392**	**18.5**	**740**	**4.0**	**2211**	**12.0**	**636**	**3.5**	**423**	**2.3**

AIAN, American Indian and Alaska Native; *ICU*, intensive care unit; *IVF*, in vitro fertilization; *SMM*, severe maternal morbidity.

[a] Per 1000 deliveries; [b] Transfusion includes blood or red blood cells transfusion.

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TABLE 3
Adjusted odds ratios for severe maternal morbidity by race/ethnicity and mode of conception, singleton deliveries, United States, 2016–2021

		SMM		ICU admission		Blood transfusion		Eclampsia		Uterine rupture/hysterectomy	
Conception mode	Race/ethnicity	aOR[a]	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Spontaneous	Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Non-Hispanic Black	1.39	1.37–1.41	1.78	1.73–1.83	1.30	1.27–1.32	1.32	1.29–1.35	1.34	1.28–1.40
	Asian	1.04	1.02–1.07	1.34	1.28–1.40	0.95	0.92–0.98	1.09	1.04–1.13	1.18	1.10–1.26
	Hispanic	0.98	0.97–0.99	1.18	1.15–1.22	1.04	1.02–1.06	0.83	0.81–0.85	0.96	0.92–1.00
	Mixed Race	1.42	1.38–1.46	1.23	1.14–1.32	1.03	0.98–1.08	2.07	1.98–2.15	1.04	0.93–1.16
IVF	Non-Hispanic White	2.31	2.22–2.42	2.02	1.83–2.23	3.41	3.23–3.59	1.22	1.10–1.34	2.84	2.50–3.22
	Non-Hispanic Black	2.93	2.57–3.33	3.57	2.77–4.59	4.45	3.78–5.22	1.36	1.01–1.81	5.74	4.17–7.91
	Asian	2.35	2.14–2.57	3.38	2.87–3.99	3.17	2.82–3.56	1.07	0.85–1.34	3.75	2.94–5.43
	Hispanic	2.12	1.88–2.39	2.47	1.94–3.16	3.06	2.63–3.55	1.05	0.79–1.38	4.23	3.18–5.63
	Mixed Race	3.21	2.56–4.01	3.46	2.18–5.55	4.22	3.16–5.63	2.18	1.41–3.39	2.26	0.94–5.43

NHW spontaneous and NHW IVF were used as reference categories.

AOR, adjusted odds ratio; *CI*, confidence interval; *ICU*, intensive care unit; *IVF*, in vitro fertilization; *NHB*, non-Hispanic Black; *NHW*, non-Hispanic White; *SMM*, severe maternal morbidity.

[a] aORs were adjusted for maternal characteristics, including previous cesarean delivery, chronic hypertension, chronic diabetes, previous fetal death or termination of pregnancy, previous infant death, prepregnancy body mass index (BMI), maternal age (<25 and ≥35 y vs 25–34 y), parity (nulliparous, parity 1–3, parity ≥4), education (high school or higher vs less than high school), prenatal care (no prenatal care vs some prenatal care), smoking during pregnancy, and fetal sex (male vs female). American Indian and Alaska Native and Pacific Islander were excluded from the multivariable analysis due to small numbers.

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component was blood transfusion, comprising up to 30% of all SMM cases (Table 2). Rates of SMM stratified by race/ethnicity and mode of conception are shown in Table 2. In the IVF group, the highest rates of SMM were in NHB women (26.2 per 1000 singleton deliveries); while in the spontaneous conception group, the highest rates were in PI women (23.5 per 100 singleton deliveries). Among women who conceived by IVF and experienced SMM, 14.7% had two or more SMM components present, while this proportion was 8.9% among women who conceived spontaneously and experienced SMM (*P* value <.001; Supplementary Table 3).

Multivariable analysis

PI and AIAN women who conceived by IVF constituted only a relatively small group with very few cases of SMM, and therefore these two race categories were not included in multivariable analyses. Adjusted analyses using NHW women who conceived spontaneously as refence category showed that women of mixed race who conceived by IVF had the highest adjusted odds of SMM (aOR=3.21, 95% CI 2.56–4.01), followed by NHB women who conceived by IVF (aOR=2.93 95% CI 2.57–3.33; Table 3). NHB women with IVF conception had the highest relative odds of blood transfusion (aOR=4.45, 95% CI 3.78–5.22) and uterine rupture/hysterectomy (aOR=5.74, 95% CI 4.17–7.91) relative to NHW women who conceived spontaneously.

Table 4 shows AORs between race/ethnicity and composite SMM separately for spontaneous and IVF groups, with NHWs in each mode of conception as the reference category. AORs for each racial/ethnic category were similar across spontaneous and IVF groups and there were no significant interactions between race/ethnicity and IVF. Multivariable analyses of each SMM component showed that Asian women had a significantly higher aOR for ICU admission in the IVF conception group (aOR=1.34, 95% CI 1.29–1.41) compared with the spontaneous conception group (AOR=1.67, 95% CI 1.38–2.02; *P* value for interaction=.001). Racial/

TABLE 4

Adjusted odds ratios showing modification of the association between race/ethnicity and severe maternal morbidity by mode of conception, singleton deliveries, United States, 2016–2021

		SMM		ICU admission		Blood transfusion		Eclampsia		Uterine rupture/hysterectomy	
Conception mode	Race/ethnicity	aOR[a]	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Spontaneous	Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Non-Hispanic Black	1.39	1.37–1.41	1.78	1.73–1.83	1.30	1.27–1.32	1.32	1.29–1.35	**1.34**	**1.28–1.40**
	Asian	1.04	1.02–1.07	**1.34**	**1.29–1.41**	0.95	0.92–0.98	1.09	1.04–1.13	1.18	1.10–1.26
	Hispanic	0.98	0.97–1.00	1.18	1.15–1.22	1.04	1.02–1.06	0.83	0.81–0.85	**0.96**	**0.92–1.00**
	Mixed Race	1.42	1.38–1.46	1.23	1.14–1.32	1.03	0.99–1.09	2.07	1.98–2.15	1.04	0.93–1.16
IVF	Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Non-Hispanic Black	1.26	1.10–1.45	1.77	1.35–2.31	1.31	1.10–1.55	1.12	0.82–1.51	**2.02**	**1.44–2.85**
	Asian	1.01	0.92–1.12	**1.67**	**1.38–2.02**	0.93	0.82–1.06	0.88	0.68–1.13	1.32	1.01–1.73
	Hispanic	0.92	0.81–1.04	1.22	0.94–1.59	1.24	0.92–1.66	0.86	0.64–1.15	**1.49**	**1.09–2.03**
	Mixed Race	1.39	1.10–1.74	1.71	1.07–2.75	0.90	0.77–1.05	1.80	1.15–2.82	0.80	0.33–1.93

NHW spontaneous and NHW IVF were used as reference categories.

Bolded text=indicates statistically significant differences in aOR in spontaneous vs IVF conception group, that is, a statistically significant interaction (*P* values for interactions: ICU admission Asian vs NHW *P*=.0457; uterine rupture NHB vs NHW *P*=.0172, and Hispanic vs NHW *P*=.0083).

AOR, adjusted odds ratio; *CI*, confidence interval; *ICU*, intensive care unit; *IVF*, in vitro fertilization; *NHB*, non-Hispanic Black; *NHW*, non-Hispanic White; *SMM*, severe maternal morbidity.

[a] aORs were adjusted for maternal characteristics, including previous cesarean delivery, chronic hypertension, chronic diabetes, previous fetal death or termination of pregnancy, previous infant death, prepregnancy body mass index (BMI), maternal age (<25 and ≥35 y vs 25–34 y), parity (nulliparous, parity 1–3, parity ≥4), education (high school or higher vs less than high school), prenatal care (no prenatal care vs some prenatal care), smoking during pregnancy, and fetal sex (male vs female). American Indian and Alaska Native and Pacific Islander were excluded from the multivariable analysis due to small numbers.

Victory. Racial/ethnic disparity in severe maternal morbidity among women who conceived by in vitro fertilization. Am J Obstet Gynecol Glob Rep 2024.

ethnic disparities in the odds of uterine rupture/hysterectomy were larger in the IVF group, for example, compared with NHW women, NHB had an aOR of 1.34 (95% CI 1.28–1.40) for uterine rupture/hysterectomy in the spontaneous conception group vs aOR of 2.02 (95% CI 1.44–2.85) in the IVF group (*P* value for interaction=.001). Similarly, Hispanic women had an aOR of 0.96 (95% CI 0.92–1.00) for uterine rupture/hysterectomy in the spontaneous conception vs an aOR of 1.49 (95% CI 1.09–2.03) in the IVF group (*P* value for interaction<.001; Table 4).

Sensitivity analyses

Sensitivity analyses were based on live births, with additional adjustments for the type of health care insurance (information that was available not available on fetal death certificates). There was a small change in the aORs and 95% CIs for ICU admission among Asian women both in the IVF group (aOR=1.67, 95% CI 1.38–2.03) and spontaneous conception group (aOR=1.37, 95% CI 1.31–1.43) and the interaction term was not statistically significant (*P* value .001). All other results were similar to the results of analyses including all births (Supplementary Table 4).

Discussion

Our study showed a more than 2-fold elevated risk of SMM in women with singleton pregnancies who conceived by IVF relative to those who conceived spontaneously. IVF conception was associated with more than a 2-fold increased risk of eclampsia and admission to the ICU and more than a 3-fold increased risk of blood transfusion and uterine rupture/intrapartum hysterectomy. NHW and Asian women had higher rates of IVF conception compared with other race/ethnic groups. Although the overall racial/ethnic disparities in composite SMM were consistent between in the spontaneous conception and IVF groups, the disparities were greater with respect to ICU admission in Asian women who conceived by IVF and with respect to uterine rupture/intrapartum hysterectomy

in Hispanic and NHB women who conceived by IVF (relative to NHW women). Overall, IVF use was a stronger risk factor for SMM outcomes than race/ethnicity.

Our study aligns with the contemporary literature demonstrating increased risk of maternal morbidity in pregnancies conceived by IVF. A Swedish study found an elevated risk of preeclampsia, placental abruption, premature rupture of membranes, and bleeding during vaginal delivery in singleton pregnancies conceived by IVF,[27] while a study from Ontario, Canada, showed approximately 30% higher risk of SMM and/or maternal death in women who conceived by IVF.[28] The latter study included multiple pregnancies, and also reported a higher risk of SMM in women who conceived by IVF compared with other types of fertility treatments. A 3-fold elevated rate of SMM in IVF pregnancies was also reported in another Canadian study that included all multiple pregnancies and used a broader definition of SMM as well as ART (including ovulation induction treatments).[16]

With respect to racial/ethnic disparities, recent studies have shown an increased risk of maternal and perinatal mortality and SMM among some racial groups relative to NHW women.[20,29–32] We found increased rates SMM or some of its components among NHB, Asian, AIAN, PI, Hispanic, and mixed-race women relative to NHW women in both spontaneous and IVF groups. This finding is consistent for outcomes such as ICU admission and eclampsia. However, Hispanic women had similar or lower rates of some SMM components relative to NHW women. This finding may be attributed to a phenomenon recognized as the "Hispanic paradox," wherein Hispanic women experience lower risk of adverse health outcomes relative to other racial/ethnic groups.[33]

Higher risk of adverse perinatal outcomes has been observed in racialized groups who use IVF. In 2020, Seifer et al.[34] reported disparities in perinatal outcomes among NHB vs NHW women who use IVF. Other studies have reported lower pregnancy and live birth rates and greater odds of spontaneous abortion among NHB, Asian and AIAN women who conceived by IVF.[32,35] Additionally, larger racial disparities in perinatal death, preterm birth and other adverse infant health outcome have been reported in women who conceived by IVF.[23] These findings align with the increased risk of ICU admission and uterine rupture/intrapartum hysterectomy in some race/ethnicity groups relative to NHW women in our study.

Socioeconomic inequalities and institutionalized racial discrimination have been suggested as leading factors contributing to inadequate access to fertility treatments and perinatal care among vulnerable minority women.[32,36] Previous studies highlight an association between higher SES and IVF use.[37–39] In the US, an IVF cycle costs between $12,000 and $25,000[40,41]. The rates of IVF use have been reported to be lower in AIAN, NHB, and Hispanic groups,[42,43] and we also found that Asian and NHW women were more likely to give birth following IVF than other groups. NHB, Hispanic, and AIAN individuals in the US are more likely to have lower SES than NHW and Asian individuals.[44] Lower SES is associated with reduced access to high-quality maternal care and greater risk of preterm delivery, gestational diabetes, spontaneous abortion, cesarean delivery, and preeclampsia/eclampsia.[45–48] For some racial/ethnic minority groups, barriers to accessing IVF may lead to delays in fertility treatment, and higher rates of SMM and adverse pregnancy outcomes. If the access to IVF was not influenced by its cost, we would still expect similar racial/ethnic disparities as in general population, because high-quality maternity care after IVF may still be subject to race- and ethnicity-related barriers.

Strengths and limitations

The strengths of our study include the population-based design that enhanced generalizability and reduced selection bias compared with hospital-based studies. The large study size increased the statistical power necessary to assess rare outcomes. The data that we utilized have been consistently collected by trained personnel using standard live birth and fetal death certificates over many years and provided detailed information about many potential confounders. Multivariable analyses adjusted for unequal distribution of risk factors for SMM across race/ethnicity and mode of conception strata.

Our study has several limitations. First, the self-reported information on IVF conception is subject to misclassification. However, such misclassification could be relatively similar across race/ethnicity groups. Second, data about postpartum hemorrhage, uterine rupture/hysterectomy, and health care insurance were not included in fetal death certificates. Thus, the results with respect to SMM may be underestimated in our study, as SMM is associated with stillbirth. Third, we did not have data on other SMM conditions (eg, pulmonary embolism, shock, and severe cardiovascular events), and information regarding the severity of SMM components (eg, the number of units of blood transfused). Even though severe morbidity components are potentially life-altering events and thus more likely to be noted and documented, studies show that SMM is seriously underreported on birth certificates.[49] A recent validation study, which showed differential underreporting of maternal morbidity by race/ethnicity,[50] also suggests that racial/ethnic disparities in our study may be underestimated. Further studies are required to assess the impact of potentially differential misclassification of SMM and other information on birth certificates on the associations between race/ethnicity, IVF, and SMM. Third, we also lacked detailed information on social determinants of health such as access to healthcare, immigration status, and experience of racism, and how this affected pregnancy and maternity care in each group. These factors contribute to SMM, and future studies should further examine their impact in connection to IVF. Fourth, we present many statistical comparisons; thus, the *P* values and CI should be interpreted with caution. Lastly, we were not able to assess

the relative risks of SMM components in PI and AIAN women who conceived by IVF due to a very small number of SMM women from these racial/ethnic groups.

Conclusion

Our large population-based study showed that SMM rates were elevated in women who conceived by IVF, and the association between IVF and SMM was stronger than the association between race/ethnicity and SMM. In some racial/ethnic groups, larger disparities in uterine rupture/hysterectomy and ICU admission were found in women who conceived by IVF as compared with the same disparities among women who conceived spontaneously. Women of all race/ethnicities who are considering IVF should be informed and counseled regarding the risks for SMM before the IVF process is initiated. Further research is needed to assess the role of prenatal and intrapartum care and the root causes of disparities in SMM by race/ethnicity. ■

CRediT authorship contribution statement

Jenna Victory: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Sid John:** Writing – review & editing. **Li Qing Wang:** Writing – review & editing. **Johanna Koegl:** Writing – review & editing. **Lindsay L Richter:** Writing – review & editing, Project administration. **Hamideh Bayrampour:** Writing – review & editing, Methodology, Conceptualization. **K.S. Joseph:** Writing – review & editing, Writing – original draft. **Sarka Lisonkova:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2024.100367.

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