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Adverse pregnancy, delivery and neonatal outcomes across different advanced maternal ages: A population-based retrospective cohort study

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ABSTRACT

Objective: Characterize the risk for adverse pregnancy, delivery and neonatal outcomes among different advanced maternal ages (AMA).

Study design: We conducted a population-based retrospective cohort study using data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample to characterize adverse pregnancy, delivery and neonatal outcomes among different AMA groups. Patients aged 44–45 (n = 19,476), 46–49 (n = 7528) and 50–54 years (n = 1100) were compared to patients aged 38–43 years (n = 499,655). A multivariate logistic regression analysis adjusted for statistically significant confounding variables.

Results: With advancing age, rates of chronic hypertension, pregestational diabetes, thyroid disease and multiple gestation increased ($p < 0.001$). The adjusted risk of hysterectomy and need for blood transfusion substantially increased with advancing age, reaching up to an almost 5-fold (aOR, 4.75, 95 % CI, 2.76–8.19, $p < 0.001$) and 3-fold (aOR, 3.06, 95 % CI, 2.31–4.05, $p < 0.001$) increased risk, respectively, in patients aged 50–54 years. The adjusted risk of maternal death increased 4-fold in patients aged 46–49 years (aOR, 4.03, 95 % CI, 1.23–13.17, $p = 0.021$). Adjusted risks of pregnancy-related hypertensive disorders, including gestational hypertension and preeclampsia, increased by 28–93 % across advancing age groups ($p < 0.001$). Adjusted neonatal outcomes demonstrated up to a 40 % elevated risk of intrauterine fetal demise in patients aged 46–49 years (aOR, 1.40, 95 % CI, 1.02–1.92, $p = 0.04$) and a 17 % increased risk of having a small for gestational age neonate in patients aged 44–45 years (aOR, 1.17, 95 % CI, 1.05–1.31, $p = 0.004$).

Conclusions: Pregnancies at AMA are at increased risk for adverse outcomes, particularly for pregnancy-related hypertensive disorders, hysterectomy, blood transfusion, and maternal and fetal mortality. Although comorbidities associated with AMA influence the risk of complications, AMA was demonstrated to be an independent risk factor for major complications, with its impact varying across ages. This data imparts clinicians with the ability to provide more specific counseling to patients of varied AMA. Older patients seeking to conceive must be counseled regarding these risks in order to make well-informed decisions.

Introduction

Over the last three decades, pregnancy at advanced maternal age (AMA) has been increasing in frequency [1]. According to a report from the Center for Disease Control and Prevention, the prevalence of first births among women aged 35 years and over in the United States rose 23 % (from 7.4 % to 9.1 %) between 2000 and 2014 [2]. From 2006 to 2015, the proportion of births increased 5 % for women 35–39, 8 % for women 40–44, and 26 % for women 45–54 years old [3]. Many studies have demonstrated the increased risk for adverse outcomes in AMA patients [1,3–6]. However, few studies stratified these risks by maternal age over 35 years, and in studies that did, extremely AMA patients (over 45 years old) were grouped into single and/or broad age categories [4,7–9]. Furthermore, studies often compared their AMA groups to non-AMA controls, and studies examining the differential risks between different AMA subgroups are few [4,5,8,10,11]. Few studies examined

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neonatal outcomes [4,7,10]. In order to address these knowledge gaps, our study sought to characterize the differences in adverse pregnancy, delivery and neonatal outcomes between several AMA subgroups and a control of patients at the lower extreme of AMA. This information would be useful to clinicians counseling their varied AMA patients.

Materials and methods

We conducted a retrospective population-based study using data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample from 2004 to 2014. This database, which represents the largest inpatient sample database in the United States, provides annual information relating to approximately seven million inpatient stays. This data represents 20 % of admissions to American hospitals annually and geographically represents over 96 % of the American population.

We divided groups of pregnant patients based on age at the time of delivery into 38–43 (control group), 44–45, 46–49 and 50–54 years, inclusive. We used the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes for delivery-related discharge diagnoses (650.xx, 677.xx, 651.xx-676.xx where the fifth digit is 0, 1, or 2), and birth-related procedural diagnosis (72.x, 73.x, 74.0–74.2). Our study group was limited only to those admissions that ended with either delivery or maternal death to ensure that multiple admissions in the same pregnancy were excluded.

Each subgroup was compared to the control group to determine how each incremental increase in age affected outcomes. Baseline maternal characteristics (Table 1) and pregnancy, delivery and neonatal outcomes (Table 2) of all deliveries were identified using the appropriate ICD-9 codes. The outcome "pregnancy-induced hypertension (HTN)" includes all the pregnancy-related hypertensive disorders evaluated (gestational HTN, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on pre-existing HTN), and was included to identify significant findings that may be missed when individual pregnancy-related hypertensive disorders were analyzed independently (Table 3).

All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Chicago, USA) software. We compared baseline demographic and clinical characteristics between subgroups and controls. Next, we conducted multivariate logistic regression analysis to explore associations between each age group and clinical outcomes through the estimation of odds ratios (OR) and 95 % confidence intervals (CI). For each subgroup, the regression models were adjusted for statistically significant maternal characteristics and pathologies, as listed in Tables 4 and 5.

Results

A total of 527,759 deliveries were included in our analysis: 94.7 % occurred in the control group aged 38–43 years (n = 499,655), and 3.69 % (n = 19,476), 1.43 % (n = 7528) and 0.21 % (n = 1100) occurred in the 44–45, 46–49 and 50–54 years groups, respectively.

Table 1 presents maternal characteristics of each subgroup compared to controls. Rates of chronic HTN, pregestational diabetes and thyroid disease increased with advancing age. Rates of obesity were significantly elevated in patients 50–54 years old. Rates of previous cesarean delivery (CD) decreased, while rates of multiple gestation significantly increased across advancing age groups.

The risks of requiring a hysterectomy or blood transfusion significantly increased with AMA. The unadjusted risk of peripartum hysterectomy increased up to 7-fold in the 50–54 years group; the adjusted analysis retained significance across the 46–49 (aOR, 2.62, 95 % CI, 1.89–3.63) and 50–54 (aOR, 4.75, 95 % CI, 2.76–8.19) years groups. The unadjusted risk of requiring a blood transfusion increased up to 5-fold in the 50–54 years group; the adjusted risk increased across the 44–45 (aOR, 1.24, 95 % CI, 1.08–1.42), 46–49 (aOR, 1.58, 95 % CI, 1.33–1.89), and 50–54 (aOR, 3.06, 95 % CI, 2.31–4.05) years groups.

Unadjusted data demonstrated a trend for increasing maternal mortality with advancing age, which was statistically significant only in the 46–49 years group. After adjustment, the 44–45 (aOR, 2.68, 95 % CI,

Table 1
Maternal characteristics.

Characteristics	38–43 years old N = 499,655 (94.7 %)	44–45 years old N = 19,476 (3.69 %)		46–49 years old N = 7528 (1.43 %)		50–54 years old N = 1100 (0.21 %)	
	%	%	P-value	%	P-value	%	P-value
Race							
White	56.6	57.4	< 0.001	57.5	< 0.001	60.0	< 0.001
Black	11.0	12.7		12.3		14.0	
Hispanic	18.5	16.1		16.0		11.3	
Asian and Pacific	8.6	8.3		8.1		7.2	
Native American	0.6	0.6		0.6		0.6 (n = 6)	
Other	4.8	4.9		5.4		6.8	
Income quartiles			< 0.001		< 0.001		0.692
Less than 39,000	17.6	17.3		17.0		17.3	
$39,000–47,999	20.1	19.0		19.4		19.3	
$48,000–62,999	25.4	25.1		23.1		24.2	
$63,000 or more	36.9	38.6		40.5		39.1	
Insurance plan type			0.003		< 0.001		< 0.001
Medicare	0.8	1.0		1.5		3.5	
Medicaid	23.5	23.8		19.3		13.2	
Private including HMO	70.3	69.6		73.0		77.0	
Self-pay	3.1	3.4		3.9		3.6	
No charge	0.2	0.1		0.2		0.3 (n = 3)	
Other	2.1	2.0		2.1		2.4	
Obesity (pre-pregnancy BMI > 30 kg/m^2)	4.1	4.2	0.547	3.8	0.110	5.4	0.039
Previous CD	25.9	24.8	< 0.001	22.5	< 0.001	20.2	< 0.001
Smoking during pregnancy	3.1	3.2	0.692	2.2	< 0.001	5.7	< 0.001
Chronic HTN	4.7	7.2	< 0.001	8.2	< 0.001	17.7	< 0.001
Pregestational DM	2.1	2.7	< 0.001	3.3	< 0.001	6.8	< 0.001
Illicit Drug use	1.0	1.1	0.227	0.5	< 0.001	1.0	0.999
Thyroid disease	5.5	7.2	< 0.001	9.1	< 0.001	11.6	< 0.001
Multiple gestation	2.6	5.3	< 0.001	11.5	< 0.001	14.2	< 0.001

BMI: body mass index; CD: cesarean delivery; DM: diabetes mellitus; HMO: Health Maintenance Organization; HTN: hypertension.

Table 2
Pregnancy, delivery, other maternal and neonatal outcomes (%).

	38–43 years old N = 499,655 (94.7 %)	44–45 years old N = 19,476 (3.69 %)	46–49 years old N = 7528 (1.43 %)	50–54 years old N = 1100 (0.21 %)
Pregnancy outcomes				
Pregnancy-induced HTN*	8.8	11.9	16.7	17.5
Gestational HTN	3.5	4.4	5.2	5.6
Preeclampsia	4.1	5.7	9.1	9.0
Eclampsia	0.1	0.1	0.1 (n = 9)	0.0 (n = 0)
Preeclampsia and eclampsia superimposed on pre-existing HTN	1.3	1.9	2.4	3.0
GDM	12.4	15.2	15.4	14.2
Placenta previa	1.3	1.9	2.4	2.3
Delivery outcomes				
PPROM	1.4	1.7	2.3	1.6
Preterm delivery	8.4	11.1	14.3	13.2
Abruptio placenta	1.4	1.7	1.8	1.6
Chorioamnionitis	1.4	1.5	1.4	1.3
Operative vaginal delivery	4.4	4.7	4.7	15.6
CD	45.7	52.6	60.1	55.4
SVD	49.9	42.7	35.2	29.0
Hysterectomy	0.3	0.4	0.9	1.8
PPH	3.1	4.0	4.7	4.0
Wound complications	0.7	0.8	1.1	1.6
Maternal death	0.0 (n = 75)	0.0 (n = 6)	0.1 (n = 8)	0.1 (n = 1)
Transfusion	1.3	2.1	3.1	6.0
Other maternal outcomes				
Maternal infection	1.8	1.9	1.8	1.5
DVT	0.1	0.1	0.1 (n = 6)	0.4 (n = 4)
Pulmonary embolism	0.0 (n = 156)	0.0 (n = 6)	0.0 (n = 3)	0.0 (n = 0)
VTE	0.1	0.1	0.1 (n = 9)	0.4 (n = 4)
DIC	0.3	0.4	0.5	0.6 (n = 7)
Neonatal outcomes				
SGA	2.3	3.1	3.6	3.7
IUFD	0.6	0.9	0.9	0.5 (n = 5)
Congenital anomalies	0.5	0.5	0.5	0.8 (n = 9)

CD: cesarean delivery; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; GDM: gestational diabetes mellitus; HTN: hypertension; IUFD: intrauterine fetal demise; PPH: post-partum hemorrhage; PPROM: preterm premature rupture of membranes; SGA: small for gestational age (birth weight less than the tenth percentile for gestational age); SVD: spontaneous vaginal delivery; VTE: venous thromboembolism.
* *"Pregnancy-induced HTN" includes gestational HTN, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on pre-existing HTN.*

1.06–6.79) and 46–49 (aOR, 4.03, 95 % CI, 1.23–13.17) years groups demonstrated a significant increased risk of maternal death.

The unadjusted risk of pregnancy-related hypertensive disorders sequentially increased with advancing age, reaching a more than 2-fold increased risk in certain subgroups. The greatest increase was observed for preeclampsia and preeclampsia and eclampsia superimposed on pre-existing HTN. After adjustment, increasing risk across advancing age groups was preserved for gestational HTN, preeclampsia and pregnancy-induced HTN as a group. Among these, the greatest risk was noted for preeclampsia across the 44–45 (aOR, 1.33, 95 % CI, 1.23–1.45), 46–49 (aOR, 1.78, 95 % CI, 1.59–1.98) and 50–54 (aOR, 1.93, 95 % CI, 1.54–2.42) years groups. The risk of preeclampsia and eclampsia superimposed on pre-existing HTN became non-significant after adjustment. No significant trend was observed for eclampsia.

Odds of achieving a spontaneous vaginal delivery (SVD) decreased steadily as age advanced with a corresponding increased risk of CD in patients up to 54 years old. Odds for operative vaginal delivery increased 4-fold in patients aged 50–54 years (aOR, 4.19, 95 % CI, 3.48–5.04).

The unadjusted risk of placenta previa, preterm delivery (PTD), wound complications and disseminated intravascular coagulation (DIC) significantly increased across all subgroups. Of these, wound complications and DIC demonstrated the most notable risks, reaching more than a 2-fold increased risk in the 50–54 years group. After adjustment, risk remained significant only for placenta previa in the 44–45 (aOR, 1.39, 95 % CI, 1.20–1.60) and 46–49 (aOR, 1.60, 95 % CI, 1.31–1.96) years groups.

Unadjusted odds of gestational diabetes mellitus (GDM), post-partum hemorrhage (PPH), preterm premature rupture of membranes (PPROM), and abruptio placenta significantly increased in the 44–45 and 46–49 years groups. After adjustment, only GDM and PPH retained significance in these subgroups. The risk of GDM increased in patients aged 44–45 (aOR, 1.27, 95 % CI, 1.20–1.34) and 46–49 (aOR, 1.27, 95 % CI, 1.17–1.38) years. The risk of PPH increased in the 44–45 (aOR, 1.19, 95 % CI, 1.08–1.32) and 46–49 (aOR, 1.29, 95 % CI, 1.12–1.48) years groups.

The unadjusted risk of having a small for gestational age (SGA) neonate increased sequentially across subgroups. After adjustment, elevated risk was maintained only in the 44–45 years group (aOR, 1.17, 95 % CI, 1.05–1.31). The risk of intrauterine fetal demise (IUFD) significantly increased for the 44–45 (aOR, 1.33, 95 % CI, 1.08–1.63) and 46–49 (aOR, 1.40, 95 % CI, 1.02–1.92) years groups. Congenital anomaly risk was non-significant across subgroups.

Discussion

Whether adjusted or unadjusted risks should be considered is a complex issue since we adjusted for higher rates of chronic disease, which are inherent underlying risks in older pregnant populations. The following discussion will focus on adjusted risks, as these will more appropriately represent the effect of AMA on the outcomes measured.

Risks of requiring a hysterectomy or blood transfusion drastically increased with AMA, reaching an almost 5-fold and 3-fold increased risk, respectively, in the adjusted analysis for patients 50–54 years old. Patients 44–49 years old were also at increased risk of having a placenta previa and PPH. Sheen et al. demonstrated an increasing risk for hysterectomy with AMA, reaching a rate of 103 hysterectomies per 10,000 deliveries in patients 45–54 years old [3]. Other studies also reported elevated risks for placenta previa and antepartum hemorrhage in patients over 45 years old and a strong correlation between AMA (> 40 years), PPH and need for transfusion [8,12]. These findings are likely explained by physicians' lower threshold for performing hysterectomies in AMA patients with PPH, especially in the presence of risk factors such as placenta previa. These risks must be communicated with AMA patients given the elevated morbidity and mortality associated with peripartum hysterectomies [13].

The unadjusted risk of maternal death strikingly increased with AMA, reaching up to a 7-fold increased odds in patients aged 46–49 years. This is likely a result of the increased prevalence of coexisting medical conditions and obstetrical complications seen in this population. However, even after adjusting for comorbidities, increased risk was preserved in patients aged 44–49 years, suggesting that AMA is an independent risk factor for maternal mortality. The 50–54 years group did not demonstrate an increased mortality rate, which is attributable to this subgroup's relatively smaller sample size in respect to this rare outcome. Therefore, our study was underpowered to detect a statistically significant difference in this subgroup.

The adjusted analysis demonstrated an increased risk for gestational HTN and preeclampsia with AMA. Baseline maternal characteristics also showed an increasing trend for chronic HTN with advancing age, reaching a prevalence of 18 % in patients 50–54 years old. Given that chronic HTN is a well-known risk factor for the development of

Table 3
Pregnancy, delivery, other maternal and neonatal outcomes (unadjusted).

	44–45 years old N = 19,476		46–49 years old N = 7528		50–54 years old N = 1100	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Pregnancy outcomes						
Pregnancy-induced HTN*	1.40 (1.34–1.46)	< 0.001	2.08 (1.95–2.21)	< 0.001	2.19 (1.88–2.57)	< 0.001
Gestational HTN	1.27 (1.18–1.36)	< 0.001	1.51 (1.36–1.67)	< 0.001	1.63 (1.26–2.11)	< 0.001
Preeclampsia	1.41 (1.33–1.50)	< 0.001	2.36 (2.18–2.56)	< 0.001	2.33 (1.89–2.86)	< 0.001
Eclampsia	1.43 (0.88–2.33)	0.151	1.96 (1.01–3.80)	0.047	N/A	N/A
Preeclampsia and eclampsia superimposed on pre-existing HTN	1.50 (1.35–1.67)	< 0.001	1.87 (1.61–2.17)	< 0.001	2.37 (1.68–3.36)	< 0.001
GDM	1.27 (1.22–1.32)	< 0.001	1.29 (1.21–1.37)	< 0.001	1.17 (0.99–1.39)	0.064
Placenta previa	1.42 (1.28–1.58)	< 0.001	1.79 (1.54–2.08)	< 0.001	1.71 (1.15–2.54)	0.008
Delivery outcomes						
PPROM	1.16 (1.04–1.30)	0.009	1.60 (1.37–1.86)	< 0.001	1.15 (0.72–1.84)	0.554
Preterm delivery	1.35 (1.29–1.42)	< 0.001	1.81 (1.70–1.93)	< 0.001	1.65 (1.39–1.97)	< 0.001
Abruptio placenta	1.25 (1.12–1.40)	< 0.001	1.27 (1.07–1.51)	0.007	1.19 (0.74–1.89)	0.476
Chorioamnionitis	1.05 (0.94–1.19)	0.378	0.95 (0.78–1.16)	0.614	0.88 (0.52–1.50)	0.648
Operative vaginal delivery	1.06 (0.99–1.13)	0.100	1.07 (0.96–1.19)	0.215	4.01 (3.40–4.72)	< 0.001
CD	1.32 (1.28–1.36)	< 0.001	1.79 (1.71–1.87)	< 0.001	1.47 (1.31–1.66)	< 0.001
SVD	0.75 (0.73–0.77)	< 0.001	0.55 (0.52–0.57)	< 0.001	0.41 (0.36–0.47)	< 0.001
Hysterectomy	1.71 (1.38–2.13)	< 0.001	3.38 (2.63–4.33)	< 0.001	6.79 (4.30–10.73)	< 0.001
PPH	1.31 (1.21–1.40)	< 0.001	1.55 (1.39–1.72)	< 0.001	1.30 (0.96–1.76)	0.086
Wound complications	1.23 (1.05–1.44)	0.009	1.64 (1.32–2.04)	< 0.001	2.42 (1.52–3.86)	< 0.001
Maternal death	2.05 (0.89–4.72)	0.090	7.09 (3.42–14.70)	< 0.001	6.06 (0.84–43.63)	0.074
Transfusion	1.55 (1.40–1.71)	< 0.001	2.34 (2.05–2.68)	< 0.001	4.71 (3.66–6.06)	< 0.001
Other maternal outcomes						
Maternal infection	1.09 (0.98–1.21)	0.102	1.00 (0.84–1.19)	0.981	0.88 (0.54–1.41)	0.587
DVT	1.41 (0.90–2.21)	0.135	1.09 (0.49–2.45)	0.827	5.01 (1.87–13.45)	0.001
Pulmonary embolism	0.99 (0.44–2.23)	0.974	1.28 (0.41–4.00)	0.675	N/A	N/A
VTE	1.33 (0.90–1.97)	0.157	1.19 (0.62–2.30)	0.605	3.63 (1.36–9.73)	0.010
DIC	1.41 (1.13–1.77)	0.003	1.72 (1.24–2.37)	< 0.001	2.17 (1.03–4.57)	0.042
Neonatal outcomes						
SGA	1.39 (1.28–1.51)	< 0.001	1.63 (1.44–1.84)	< 0.001	1.68 (1.23–2.29)	0.001
IUFD	1.40 (1.20–1.63)	< 0.001	1.43 (1.12–1.82)	0.004	0.71 (0.29–1.70)	0.437
Congenital anomalies	1.07 (0.87–1.31)	0.548	1.06 (0.76–1.47)	0.748	1.81 (0.94–3.50)	0.076

CD: cesarean delivery; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; GDM: gestational diabetes mellitus; HTN: hypertension; IUFD: intrauterine fetal demise; PPH: post-partum hemorrhage; PPROM: preterm premature rupture of membranes; SGA: small for gestational age (birth weight less than the tenth percentile for gestational age); SVD: spontaneous vaginal delivery; VTE: venous thromboembolism.
* *"Pregnancy-induced HTN" includes gestational HTN, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on pre-existing HTN.*

pregnancy-related hypertensive disorders, older patients that are at greater risk for chronic HTN are also at greater risk for related complications in pregnancy, including preeclampsia [7]. This explains why the risks were comparatively higher in the unadjusted analysis, which did not control for chronic HTN. The adjusted risk of preeclampsia and eclampsia superimposed on pre-existing HTN was non-significant, which is intuitively due to the removal of the effect of chronic HTN. No significant trends were observed for eclampsia, which is likely due to the rarity of this syndrome with proper prenatal care.

In other studies, women that were screened to exclude pre-existing diseases such as HTN had a trend of favorable pregnancy outcomes even at 50–65 years of age, suggesting that pre-gestational health status, and not solely AMA, plays a role in predicting the risk of adverse outcomes [7,12]. Therefore, screening older patients for underlying HTN

Table 4
Pregnancy outcomes (adjusted).

	44–45 years old[a] N = 19,476		46–49 years old[b] N = 7528		50–54 years old[c] N = 1100	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Pregnancy-induced HTN*	1.30 (1.23–1.38)	< 0.001	1.67 (1.54–1.81)	< 0.001	1.54 (1.30–1.84)	< 0.001
Gestational HTN	1.28 (1.17–1.40)	< 0.001	1.51 (1.32–1.72)	< 0.001	1.72 (1.30–2.27)	< 0.001
Preeclampsia	1.33 (1.23–1.45)	< 0.001	1.78 (1.59–1.98)	< 0.001	1.93 (1.54–2.42)	< 0.001
Eclampsia	0.85 (0.37–1.91)	0.686	1.35 (0.50–3.67)	0.557	N/A	N/A
Preeclampsia and eclampsia superimposed on pre-existing HTN	1.13 (0.98–1.31)	0.098	1.22 (0.98–1.51)	0.072	0.73 (0.48–1.09)	0.124
GDM	1.27 (1.20–1.34)	< 0.001	1.27 (1.17–1.38)	< 0.001	1.11 (0.92–1.34)	0.297
Placenta previa	1.39 (1.20–1.60)	< 0.001	1.60 (1.31–1.96)	< 0.001	1.44 (0.93–2.22)	0.105

GDM: gestational diabetes mellitus; HTN: hypertension.
* *"Pregnancy-induced HTN" includes gestational HTN, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on pre-existing HTN.*
a- Pregnancy outcomes for ages 44–45: adjusted by race, insurance plan type, income quartiles, previous cesarean delivery, thyroid disease, chronic HTN, multiple gestation, pregestational DM.
b- Pregnancy outcomes for ages 46–49: adjusted by race, insurance plan type, income quartiles, previous cesarean delivery, thyroid disease, chronic HTN, multiple gestation, pregestational DM, illicit drug use, smoking during pregnancy.
c- Pregnancy outcomes for ages 50–54: adjusted by race, insurance plan type, pre-pregnancy BMI > 30 kg/m^2, previous cesarean delivery, thyroid disease, chronic HTN, multiple gestation, pregestational DM, smoking during pregnancy.

could help clinicians provide appropriate counseling regarding their risk of developing pregnancy-related hypertensive disorders [7]. However, the risk of gestational HTN and preeclampsia increased with AMA despite controlling for chronic HTN, suggesting that AMA independently increases the risk of these complications.

The likelihood of SVD decreased while CD rates increased with AMA, likely due to increased failed trials of labor (TOL) and CD in this population. Studies have demonstrated that patients over 50 years are less likely to undergo TOL and more likely to have an elective CD, especially if nulliparous [7,10]. It remains unclear why odds of CD in the 50–54 years group increased to a lesser degree than in the 46–49 years group with a corresponding 4-fold increased risk for operative vaginal delivery. Interestingly, one study found that although nulliparous women over 50 years were more likely to undergo CD, 74 % of those that underwent TOL had a successful vaginal delivery; this rate increased to 89 % in multiparous women [10]. It is not mentioned if these were assisted vaginal deliveries, but extrapolating from our data, it is highly likely they were. The authors concluded that neither a TOL nor a prelabour CD is significantly associated with adverse outcomes, suggesting that AMA patients could safely attempt a TOL [10]. Ultimately, decisions regarding mode of delivery should be made between the patient and their physician, taking into account the patient's comorbidities and obstetrical history, and after discussion of risks associated with operative vaginal deliveries versus elective and emergency CD.

The risk of GDM increased only in patients 44–49 years of age. However, we noted a significant trend for increasing prevalence of pregestational diabetes with AMA, affecting 6.8 % of patients aged 50–54 years, a rate twice that observed in younger subgroups. The non-significant risk of GDM in this subgroup is likely explained by the fact that they were more likely to already have pregestational diabetes, excluding them from being diagnosed with GDM. Therefore, patients of AMA are at greater risk for diabetes, whether it be pre-pregnancy or gestational. This is supported by many other studies that found strong associations between AMA and both pregestational and gestational diabetes [1,3–5,10,14].

Adjusted data revealed that patients aged 44–45 and 44–49 are at increased risk of having SGA neonates and IUFD, respectively. The unadjusted analysis demonstrated a more pronounced trend for these outcomes, which is intuitively due to the effects imparted by maternal and gestational comorbidities associated with AMA. One study demonstrated a significantly elevated risk for SGA but not IUFD across increasing maternal ages from 30 to over 45 years [4]. Other reports have shown that AMA patients are at an increased risk for stillbirths, perinatal mortalities, low birth weight and SGA neonates [1,6,8,11,15]. Our findings demonstrate the significant impact of AMA on the risk of IUFD relative to other neonatal outcomes. This risk should be communicated with patients as it may have important implications for delivery planning.

Our study did not demonstrate significant risk of neonatal congenital anomalies. Some studies demonstrated mild or no increased risk of congenital anomalies in neonates born to AMA patients [1,16,17], while others demonstrated increased risk [18,19]. Although we did not stratify for conception method, it can be assumed that a considerable proportion of AMA patients conceived using donor oocytes, which can influence the risk of congenital anomalies. More studies are needed to clarify the neonatal risks associated with AMA.

Advantages of our study include its large sample size and its examination of both maternal and neonatal outcomes. In contrast to the majority of other studies, we deciphered differences in risk between different AMA groups compared to patients at the lower extreme of AMA; the majority of pre-existent studies grouped AMA patients into broader age subgroups or compared them to non-AMA controls.

The main limitation of our study was our inability to control for mode of conception, whether it be spontaneous or in-vitro fertilization with donor or autologous oocytes. These are likely to exert important effects on pregnancy, delivery and neonatal outcomes. Secondly, we were unable to examine the effects of AMA on multiple gestation given the small sample size. Thirdly, since our study is retrospective and depends on ICD diagnosis codes, there is a potential for information bias with the misuse of more unfavorable diagnoses for AMA patients. Lastly, although one could argue that controls should have included women as young as 35 years old, this would have likely only accentuated our results and not have changed the significant results we detected.

Conclusions

With recent advances in assisted reproductive technologies, many more patients are delaying childbearing. However, these developments

Table 5
Delivery, other maternal and neonatal outcomes (adjusted).

	44–45 years old[a] N = 19,476		46–49 years old[b] N = 7528		50–54 years old[c] N = 1100	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Delivery outcomes						
PPROM	1.05 (0.91–1.22)	0.493	1.08 (0.87–1.34)	0.491	0.78 (0.47–1.29)	0.336
Preterm delivery	1.06 (0.99–1.13)	0.102	1.06 (0.96–1.18)	0.222	0.84 (0.68–1.05)	0.120
Abruptio placenta	1.10 (0.95–1.29)	0.212	1.07 (0.84–1.36)	0.576	0.96 (0.58–1.61)	0.878
Chorioamnionitis	0.98 (0.84–1.15)	0.792	0.76 (0.58–0.99)	0.043	0.74 (0.42–1.31)	0.297
Operative vaginal delivery	1.05 (0.96–1.16)	0.293	1.08 (0.93–1.26)	0.319	4.19 (3.48–5.04)	< 0.001
CD	1.36 (1.30–1.42)	< 0.001	1.81 (1.68–1.95)	< 0.001	1.40 (1.20–1.63)	< 0.001
SVD	0.74 (0.71–0.77)	< 0.001	0.55 (0.51–0.59)	< 0.001	0.39 (0.33–0.46)	< 0.001
Hysterectomy	1.23 (0.92–1.66)	0.166	2.62 (1.89–3.63)	< 0.001	4.75 (2.76–8.19)	< 0.001
PPH	1.19 (1.08–1.32)	< 0.001	1.29 (1.12–1.48)	< 0.001	0.87 (0.62–1.24)	0.445
Wound complications	1.15 (0.93–1.43)	0.209	1.31 (0.97–1.77)	0.077	1.50 (0.84–2.67)	0.169
Maternal death	2.68 (1.06–6.79)	0.038	4.03 (1.23–13.17)	0.021	N/A	N/A
Transfusion	1.24 (1.08–1.42)	0.002	1.58 (1.33–1.89)	< 0.001	3.06 (2.31–4.05)	< 0.001
Other maternal outcomes						
Maternal infection	1.03 (0.89–1.18)	0.728	0.86 (0.68–1.09)	0.206	0.74 (0.44–1.24)	0.251
DVT	0.87 (0.41–1.86)	0.725	1.15 (0.42–3.13)	0.783	3.47 (1.10–10.97)	0.034
Pulmonary embolism	0.49 (0.12–2.02)	0.326	1.43 (0.44–4.63)	0.555	N/A	N/A
VTE	0.78 (0.40–1.53)	0.472	1.32 (0.62–2.82)	0.478	2.35 (0.75–7.39)	0.145
DIC	1.20 (0.90–1.60)	0.221	1.16 (0.77–1.76)	0.474	1.19 (0.49–2.91)	0.696
Neonatal outcomes						
SGA	1.17 (1.05–1.31)	0.004	1.07 (0.91–1.25)	0.443	0.93 (0.66–1.30)	0.669
IUFD	1.33 (1.08–1.63)	0.008	1.40 (1.02–1.92)	0.040	0.66 (0.27–1.59)	0.353
Congenital anomalies	0.98 (0.76–1.26)	0.868	0.96 (0.65–1.42)	0.837	1.31 (0.62–2.78)	0.477

CD: cesarean delivery; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; GDM: gestational diabetes mellitus; HTN: hypertension; IUFD: intrauterine fetal demise; PPH: post-partum hemorrhage; PPROM: preterm premature rupture of membranes; SGA: small for gestational age (birth weight less than the tenth percentile for gestational age); SVD: spontaneous vaginal delivery; VTE: venous thromboembolism.
a- Delivery, other maternal and neonatal outcomes for ages 44–45: adjusted by race, insurance plan type, income quartiles, previous cesarean delivery, thyroid disease, chronic HTN, multiple gestation, pregestational DM, pregnancy-induced HTN, gestational DM and placenta previa.
b- Delivery, other maternal and neonatal outcomes for ages 46–49: adjusted by race, insurance plan type, income quartiles, previous cesarean delivery, thyroid disease, chronic HTN, multiple gestation, pregestational DM, illicit drug use, smoking during pregnancy, pregnancy-induced HTN, gestational DM and placenta previa.
c- Delivery, other maternal and neonatal outcomes for ages 50–54: adjusted by race, insurance plan type, pre-pregnancy BMI > 30 kg/m^2, previous cesarean delivery, thyroid disease, chronic HTN, multiple gestation, pregestational DM, smoking during pregnancy, pregnancy-induced HTN.

come at the cost of increased adverse outcomes, particularly for pregnancy-related hypertensive disorders, hysterectomy, blood transfusion, and maternal and fetal mortality. Although comorbidities associated with AMA influence the risk of complications, AMA was demonstrated to be an independent risk factor for major complications, with its impact varying across ages. This data imparts clinicians with the ability to provide more specific counseling to patients of varied AMA. Older patients seeking to conceive must be counseled regarding these risks in order to make well-informed decisions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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