Published in final edited form as:

J Matern Fetal Neonatal Med. 2016 ; 29(9): 1485–1490. doi:10.3109/14767058.2015.1051955.

Gestational age-specific neonatal morbidity among pregnancies complicated by advanced maternal age: a population-based retrospective cohort study

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Abstract

OBJECTIVE—Compare significant neonatal morbidity frequency differences in advanced maternal age (AMA) versus non-AMA pregnancies, assessing which gestational week is associated with the lowest morbidity risk.

METHODS—Population-based retrospective cohort study. Adverse neonatal outcome frequency differences were stratified by each week of gestation. Multivariate logistic regression estimated the relative risk (RR) of composite neonatal morbidity for women ages 35–39, 40–44, 45–49, and 50–55 vs. 18–34 years, adjusted sequentially for relevant risk factors.

RESULTS—Neonatal morbidity decreased with each advancing week of term gestation, lowest at 39 weeks for all groups. Adverse neonatal outcome risk for births to AMA women increased at 40 weeks: 35–39 years adjRR 1.12 [1.01–1.24], 40 years 1.24 [1.01–1.52]. Each older maternal age category had increased risk for overall neonatal morbidity: 35–39 years adjRR 1.11 [95% CI 1.08–1.15], 40–44 years 1.21 [95% CI 1.14–1.29], and 45–49 years 1.34 [95% CI 1.05–1.69].

CONCLUSIONS—Lowest neonatal morbidity risk is at 39 weeks gestation with a significantly increased risk observed thereafter, especially in women 40 years.

Keywords

Adverse neonatal outcomes; gestational week of delivery; advanced maternal age

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DECLARATION OF INTEREST: The authors disclose no conflict of interest.

INTRODUCTION

Over the past several decades, there has been an increasing trend of delayed childbearing in women of industrialized nations¹. The evolving social paradigms and advancements in assisted reproductive medicine have contributed to the higher incidence of pregnancy in women of advanced maternal age (AMA). However, aging is associated with an increased prevalence of maternal medical disorders that may adversely impact the health of the pregnancy². AMA women have increased rates of hypertensive disorders, diabetes, placental abruption and abnormal placental locations^{3,4}. This is especially true in women over the age of 40^{5,6}.

The overall health of a newborn at term may be quantified by measuring how frequently common adverse newborn complications occur with birth at each week of gestational age. Some of the most easily measured objective indicators of poor newborn health immediately after delivery include low 5 minute Apgar score, NICU admission, transfer to a tertiary care facility, and presence of newborn seizures or need for ventilator support. There is a paucity of published data quantifying the frequency of clinically important neonatal morbidities by week of gestational age in women of advancing maternal age.

Because gestational age at delivery impacts the risk of neonatal morbidities, the objective of this study was to compare and quantify the frequency of gestational age-specific composite neonatal morbidities of AMA women compared to women less than 35 years of age in order to identify the optimal gestational age for delivery of babies born to older mothers⁷⁻¹⁰. We hypothesize that AMA pregnancies have higher adverse neonatal outcomes than younger cohorts even without considering stillbirth.

METHODS

Study approval was obtained from the Ohio Department of Health and Human Subjects Institutional Review Board and review exemption from the University of Cincinnati, Cincinnati, Ohio. We conducted a population based retrospective cohort study using the Ohio Department of Health's birth certificate database from 2006 through 2011 to compare births to women of AMA (≥ 35 years old) and non-AMA (18–34 years old) for differences in the frequency of adverse neonatal outcomes by each week of gestation. Births less than 20 and greater than 42 weeks gestation, multifetal pregnancies, congenital anomalies, chromosomal abnormalities, and maternal ages less than 18 years and greater than 60 years old were excluded from the study cohort. These exclusions share an increased risk for adverse neonatal outcomes regardless of inclusion in either group and would not represent the risks and outcomes specifically of AMA pregnancies focused in this study.

The primary exposure for this study was advanced maternal age, which was divided into four categories: births to women 35–39 years, 40–44 years, 45–49 years and 50–55 years old. The referent group was comprised of births to non-AMA women, 18–34 years old. Maternal age was obtained from maternal date of birth as recorded in the birth certificate at the time of delivery. The primary outcome was a composite of neonatal adverse outcomes which was defined as one or more of the following indicators of poor newborn health: Apgar

score of <7 at 5 minute evaluation, assisted ventilation >6 hours duration, NICU admission, neonatal seizures, or neonatal transport to a tertiary care facility. This study concentrated on adverse neonatal outcomes that occurred in the immediate 24 to 48 hours after delivery as all later outcomes would not be recorded on the birth certificate.

The frequency of adverse neonatal outcomes was compared between non-AMA mothers (18–34 years old) and those of AMA, 35–39 years, and 40 years old, assessed at each week of gestational age from 36–41 weeks. Because gestational ages less than 36 weeks have higher rates of NICU admission and neonatal morbidity due to prematurity and not inherently due to AMA, earlier ages were not assessed for this study. Estimated gestational age was determined from the obstetric estimate using a combination of data including the last menstrual period, ultrasound and clinical assessment, which is commonly accepted in general practice. Births to mothers at extremes of maternal age (>55 years, <0.01% of the population) and gestational age (>42 weeks, <2% of all births), which were more likely to include coding errors were excluded from the study. Birth outcomes at gestational ages less than 36 weeks were not included in the data analysis as adverse neonatal outcomes are more common in preterm neonates irrespective of maternal age and planned preterm deliveries are not advised without maternal or fetal indications.

The dataset consisted of minimal missing information for primary outcomes of interest, exposure variables and covariates (<5%). There was 3.4% missing data on maternal age, 2.3% for NICU admission, 1.1% for neonatal transport, 1.6% for neonatal seizures, and 2.3% missing data for ventilator support. The only covariate included in the study with a quantity of missing data >5% was maternal weight (10.3% missing).

Statistical analysis was performed using STATA software (STATA, release 10; Stata-Corp, College Station, TX). Demographic characteristics were compared between maternal age groups using one-way ANOVA for continuous variables and χ^2 for categorical variables. Multivariate logistic regression models were used to determine the relative risk of adverse neonatal outcome for both AMA groups versus the reference group of normal age at each gestational age between 36 and 41 weeks of gestation. Stepwise regression analyses of the composite adverse neonatal outcome was performed using multiple sequential models in order to determine the relative impact of each category of covariates on relative risk estimates in both AMA groups. Relative risk estimates within this model were adjusted for statistically significant and biologically plausible coexisting risk factors including race, maternal pre- and gestational hypertension and diabetes, marital status, education, limited prenatal care, tobacco use, parity, use of assisted reproductive technology, mode of delivery, and fetal growth restriction (FGR, estimated fetal weight <10th percentile). As coded in the birth certificate, limited prenatal care was defined as <5 visits during a woman's prenatal course. Comparisons with a probability value <0.05 or 95% confidence interval without inclusion of the null were considered statistically significant.

RESULTS

During the 6 year study period, following exclusions, 704377 (85%) births were to women 18–34 years of age. Women of advanced maternal age (AMA) included 98300 (12%) of the

total births in Ohio. These women were further stratified into 4 groups; 81199 (10%) births were to women ages 35–39, 16167 (2%) ages 40–44, 870 (0.1%) ages 45–49 and 58 (0.01%) were born to women 50–55 years of age. The demographic characteristic differences by maternal age group are displayed in Table 1. AMA women were more likely to be Caucasian, married, and have a higher prevalence of pre-gestational diabetes and chronic hypertension compared with the 18–34 years of age group. Younger women were more commonly tobacco users.

Pregnancy outcomes and maternal complication frequencies were compared by maternal age group. Women 40 years had higher rates of preterm birth (<37 weeks of gestation) compared to both women 35–39 years and the reference age group (13 vs. 11 and 10%, respectively, $p < 0.001$). AMA women were more likely to develop gestational diabetes (12 and 9 vs 5%, $p < 0.001$), have non-reassuring fetal heart rate tracing in labor (8 and 7 vs 6%, $p < 0.001$), and deliver via Cesarean method (42 and 38 vs 28%, $p < 0.001$).

The primary outcome of composite adverse neonatal outcome was compared between the AMA study groups and the referent group. The frequency of the individual neonatal morbidity within the composite, except neonatal seizures, were statistically higher in the AMA pregnancies, particularly for births to women 40 years of age (Table 2). The overall rate of composite neonatal morbidity was progressively higher for all AMA groups compared to the referent age group (8.2, 10.0, 11.1, & 12.7 vs 7.7%; $p < 0.001$).

All births to women 35 years of age had significantly higher adjusted relative risks for composite neonatal morbidity compared to the normal age referent group, despite accounting for important coexisting risk factors for adverse neonatal outcome. The risk of adverse neonatal outcome was increased 11% for births to women 35–39 years compared to normal age women, adjusted RR 1.11 (95% CI 1.08–1.15). The risk was further increased with each increasing maternal age group, $_{adj}RR$ 1.21 (95% CI 1.13–1.29) for women 40–44 years of age and 1.34 (95% CI 1.03–1.69) for women 45–49 years of age, despite adjustment for marital status, level of education, insurance status, tobacco use, quantity of prenatal care, parity, obesity, diabetes, hypertension, and FGR. More of the risk increase for adverse neonatal outcome was explained by confounding factors in older women than those age 35–39 years, however adjustment for these factors did not entirely explain the influence of maternal age on adverse neonatal outcome as risk estimates remained >1.0 for both AMA groups in the fully adjusted models (Table 3).

Gestational age impacts neonatal outcome. Gestational-age specific stratification of the frequency of composite neonatal outcome showed a decrease in morbidity with each latter week of preterm and early term gestational age with nadir at 39 weeks of gestation for births to all maternal age groups. Younger mothers (age 18–34 years) and AMA women 35–39 years had similar frequencies of adverse neonatal outcome at each week of gestational age. Women 40 years had a higher frequency of adverse neonatal outcome at each week of gestational age compared to all younger mothers, both the referent age and 35–39 years group (Figure 1). The risk increase for neonatal morbidity after 39 weeks of gestation was most remarkable for births to women 40 years old with a RR at 40 weeks of 1.24 (95% CI

1.01–1.52) and RR 1.53 (95% CI 1.12–2.08) at 41 weeks of gestation compared to women 18–34 years.

DISCUSSION

Our study demonstrates an increased frequency of composite neonatal morbidity associated with pregnancies to advanced maternal age women, most significant in parturients 40 years of age at the time of delivery. Older mothers have more concomitant pregnancy and delivery related risk factors associated with adverse neonatal outcomes. However, despite adjustment for a breadth of these comorbid conditions, AMA remains an independent risk factor for neonatal morbidity. After accounting for confounding factors, maternal age 35–39 is associated with a modest (11%) increased risk of neonatal morbidity, which is increased further for births to progressively older mothers. Although the risk for mothers 40 was higher at each week of gestation from 36–41 weeks, the risk was most pronounced at post term gestational ages 40 weeks and beyond.

Similar to previous studies, we found that older mothers were more commonly Caucasian, higher socio-economic status, and had increased rates of pre- and gestational diabetes and hypertension^{2, 11–14}. We found that at 39 weeks of gestation resulted with the lowest measure of composite morbidity, consistent with prior studies focused on stillbirth and other pregnancy complications in AMA pregnancies^{11, 15}. Nicholson et al in 2006 compared all AMA women over 34 years of age to younger age women at one institution to determine the rates of more common adverse outcomes such as cesarean section, NICU admission, 5 minute Apgar score <7, and perineal lacerations⁵. Our study included a much larger number of AMA pregnancies and focused on a composite neonatal outcome including outcomes observed by Nicholson as well as other significant neonatal complications with higher frequency, increasing the power to detect maternal age and gestational-age specific differences.

After stratifying for maternal age, we found women 40 years have a higher risk profile as compared to births to women between 35–39 years of age and those <35 years. AMA is associated with adverse neonatal outcomes even after adjusting for DM and HTN, proposing advancing age poses other risk mechanisms effecting pregnancy. Adjustments for FGR decreased the overall relative risk of neonatal morbidity. This suggests that FGR in AMA pregnancies is an important contributing pathway to adverse neonatal outcomes in these pregnancies, however is not completely explanatory. This implies that pregnant women 40 years of age may benefit from screening for fetal growth impairment in the third trimester, but even with normal growth remain at higher risk of adverse newborn outcome.

Aging is associated with physiologic changes including but not limited to reduced peripheral endothelium-dependent dilation, reduced bioavailability of nitric oxide (NO), and greater production of reactive oxygen species, which contribute to increased vascular oxidative stress¹⁶. NO is important for uterine quiescence and maintenance of pregnancy and vascular pregnancy complications¹⁷. It is plausible that the increased neonatal morbidities may be attributed to the aging physiology and the ability to accommodate the stresses of pregnancy. The degree of age-related changes is influenced by diet, exercise, and co-morbidities, which

is important counseling for all pregnancies but particularly should be emphasized in AMA women.

The major strength of this study was the large sample size which allowed for comparison of our primary outcome by week of gestational age. The inclusion of all pregnancies within Ohio over a 6 year period represents a population-based sample including different practice styles, levels of obstetric care and acuity, and demographic diversity. AMA women are a growing population within obstetrics with known risks, and investigation of maternal and neonatal outcomes are important to provide informed counseling to older mothers, and for optimal delivery timing considerations.

Limitations of this study are inherent to vital statistics research data, including the quality of data collection and entry, variables available for analysis, and ascertainment bias of outcomes. The demographic and outcome variables chosen for this study are common components described in the maternal and neonatal record, more likely representing higher quality and consistency between the chart and birth certificate ¹⁸. The exposure and components of the primary composite outcome have very little missing data in the dataset. The variables chosen for the composite neonatal outcome were clearly defined and are expected to have greater coding and entry accuracy. They were chosen specifically to represent significant neonatal morbidities and analyzed as a composite to help minimize under-reporting of individual outcomes. The increased incidence of antepartum complications, including stillbirth, has been established to be independently associated with maternal age in AMA pregnancies ^{11, 14, 19–24}.

Our study focused on more common and significant neonatal morbidities, but results were consistent emphasizing the potential increased risks for neonatal morbidity and fetal/infant death with advancing weeks of gestation. Stillbirth has been examined extensively in previous published studies in this population with a frequency of approximately 0.03% per week of gestation ^{23, 25–31}. Due to its low frequency in comparison to the weekly frequency of adverse newborn outcome, including stillbirth would have minimal contribution to our weekly composite morbidity rates and was not included in our primary, composite adverse outcome. Page et al performed a population-based retrospective cohort study with a similar design, stratifying risk of stillbirth and infant death by each additional week of expectant management, and found the fetal/infant mortality is minimized at 39 weeks ¹⁵.

Our study demonstrates a dose-response effect, in that each older maternal age category had a higher point estimate of effect, even after adjustment for confounders, and the highest frequency and relative risk of neonatal complications is more likely in parturients ≥ 40 years. It is important to note that the small number of women who delivered at ≥ 50 years in the study period was small (0.01% of the study population), limiting the statistical precision of the effect estimate, yielding a confidence interval that crossed the null value of 1.0. However, the sequentially increasing risk in each older maternal age category strengthens the overall study findings and does have biologic plausibility, supporting the probability of a cause-effect relationship in this epidemiologic analysis. These patients should be counseled about the associated risks, especially with pregnancies complicated by FGR. This study

emphasizes the potential risks of aging on the vascular physiology, which is crucial for pregnancy maintenance and optimal fetal development and outcomes.

In our practice, we provide monthly ultrasound growth assessments, recommend antenatal fetal surveillance in women ≥ 40 years of age and offer delivery at 39 weeks of gestation. Others have suggested a similar management scheme as well ³². Individualized clinical consideration should guide decisions regarding favorable delivery timing and antenatal testing as these have not yet been clearly established. Future prospective studies investigating placental differences amongst these cohorts and comparing scheduled deliveries at 39 weeks versus expectant management can provide further knowledge to the natural history of aging as it relates to pregnancy complications.

Acknowledgments

All of the analysis, interpretations, and conclusions that were derived from the data source and included in this article are those of the authors and not the Ohio Department of Health. Access to de-identified Ohio birth certificate data was provided by the Ohio Department of Health.

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Figure 1.
Frequency of composite neonatal outcome by each week of gestation

Table 1

Baseline Maternal Demographic Factors

Demographics Factors	Non-AMA 18 & <35 y/o Number (%)	AMA 35–39 y/o Number (%)	AMA 40 y/o Number (%)	P-value
Study total	704,377 (84.7)	81,199 (9.8)	17,101 (2.1)	
Age	26.0 ±4.5	36.5 ±1.4	41.4 ±1.7	<0.001
Race				
Hispanic	32,219 (4.7)	2,993 (3.9)	603 (3.7)	<0.001
Caucasian	533,394 (78.3)	65,383 (84.8)	13,476 (83.2)	
Black	115,125 (17.0)	8,736 (11.3)	2,127 (13.1)	
Parity	2 [1,3]	2 [2,3]	3 [2,4]	<0.001
Obese (BMI ≥30)	195,822 (27.8)	24,135 (29.7)	5,319 (31.1)	<0.001
Pre-gestation DM	5,091 (0.7)	1115 (1.4)	284 (1.7)	<0.001
Chronic HTN	11,285 (1.6)	2,737 (3.4)	793 (4.7)	<0.001
Tobacco use	191,282 (27.2)	11,619 (14.3)	2,424 (14.2)	<0.001

Dichotomous variables are presented as number (percent)

Continuous variables are presented as median [IQR] for non-normally distributed data and as mean +/-standard deviation for normally distributed data.

DM: diabetes mellitus; HTN: hypertension; IQR: interquartile range

Table 2

Neonatal Morbidities

Neonatal Outcomes	Non-AMA 18–34 years old	AMA 35–39 years old	AMA 40–44 years old	AMA 45–49 years old	AMA 50–55 years old	P-value
Mechanical ventilation >6 hr	4304 (0.6)	504 (0.6)	152 (1.0)	11 (1.3)	1 (1.8)	<0.001
NICU admission	36621 (5.3)	4655 (5.9)	1171 (7.4)	73 (8.5)	6 (10.9)	<0.001
5 minute Apgar <7	17260 (2.5)	2042 (2.5)	479 (3.0)	37 (4.3)	1 (1.5)	<0.001
Neonatal transport	16068 (2.3)	1923 (2.4)	493 (3.1)	31 (3.6)	2 (3.6)	<0.001
Neonatal seizure	193 (<0.1)	18 (<0.1)	8 (0.1)	1 (0.1)	0 (0)	0.19
Composite morbidity	52931 (7.7)	6535 (8.2)	15763 (10.0)	95 (11.1)	7 (12.7)	<0.001

Composite morbidity defined as 1 of the following: NICU admission, Apgar score of <7 at 5min, assisted ventilation >6 hours, neonatal seizures, or neonatal transport to a tertiary care facility.

Table 3

Logistic Regression Analysis of Composite Adverse Neonatal Outcome

Model: Covariates	AMA 35–39 years old	AMA 40–44 years old	AMA 45–49 years old	AMA 50–55 years old
Referent group: 18–34 years old	adjRR (95% CI)	adjRR (95% CI)	adjRR (95% CI)	adjRR (95% CI)
Model I Age Only	1.08 (1.05–1.10)	1.33 (1.27–1.41)	1.50 (1.21–1.85)	1.75 (0.79–3.86)
Model II Model I + Demographic Factors	1.11 (1.8–1.14)	1.36 (1.29–1.44)	1.54 (1.24–1.92)	1.55 (0.66–3.63)
Model III Model II + Social Behaviors & Socioeconomic Factors	1.25 (1.22–1.29)	1.52 (1.44–1.61)	1.77 (1.42–2.21)	1.97 (0.84–4.65)
Model IV Model III + Prenatal & Pregnancy Factors	1.29 (1.25–1.33)	1.55 (1.46–1.64)	1.84 (1.47–2.31)	1.99 (0.84–4.74)
Model V Model IV + Pregnancy Complications & Delivery Factors	1.11 (1.08–1.15)	1.23 (1.16–1.30)	1.35 (1.07–1.71)	1.40 (0.58–3.41)
Model VI Model V + FGR	1.11 (1.08–1.15)	1.21 (1.14–1.29)	1.34 (1.05–1.69)	1.18 (0.48–2.93)

Covariates included in each model: Demographic Factors = maternal race; Social Behaviors & Socioeconomic Factors = marital status, level of education, insurance status, tobacco use; Prenatal & Pregnancy Factors = limited prenatal care (<5 visits during pregnancy), parity, obese (BMI ≥30); Pregnancy Complications & Delivery Factors = route of delivery, pre-and gestational diabetes & hypertension; FGR = fetal growth restriction (birth weight <10th percentile)