Advanced Maternal Age and the Risk of Major Congenital Anomalies

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Abstract

Objective This study aims to determine if advanced maternal age (AMA) is a risk factor for major congenital anomalies, in the absence of aneuploidy.

Study Design Retrospective cohort study of all patients with a singleton gestation presenting for second trimester anatomic survey over a 19-year study period. Aneuploid fetuses were excluded. Study groups were defined by maternal age $\leq$ 34 and $\geq$ 35 years. The primary outcome was the presence of one or more major anomalies diagnosed at the second trimester ultrasound. Univariable and multivariable logistic regression analyses were used to estimate the risk of major anomalies in AMA patients.

Results Of 76,156 euploid fetuses, 2.4% ($n = 1{,}804$) were diagnosed with a major anomaly. There was a significant decrease in the incidence of major fetal anomalies with increasing maternal age until the threshold of age 35 ($p < 0.001$). Being AMA was significantly associated with an overall decreased risk for major fetal anomalies (adjusted odds ratio: 0.59, 95% confidence interval: 0.52–0.66). The subgroup analysis demonstrated similar results for women $\geq$ 40 years of age.

Conclusion AMA is associated with an overall decreased risk for major anomalies. These findings may suggest that the "all or nothing" phenomenon plays a more robust role in embryonic development with advancing oocyte age, with anatomically normal fetuses being more likely to survive.

Keywords
- advanced maternal age
- aneuploidy
- congenital anomalies
- fetal structural malformation

Over the past 20 years, there has been an increasing trend in the number of pregnancies achieved by women of advanced maternal age (AMA).[1] These women are at an increased risk of multiple pregnancy complications such as spontaneous abortion, preeclampsia, gestational diabetes, fetal growth restriction, and stillbirth.[2–6] In addition, AMA is a well-established risk factor for chromosomal abnormalities, such as trisomy 21, due to errors in meiotic nondisjunction with advancing oocyte age. Despite these known pregnancy risks, there exists limited data evaluating the relationship between being AMA and the incidence of congenital anomalies in the absence of aneuploidy.

Prior studies on this topic have generated conflicting results.[2,7–12] In a large prospective cohort study, Hollier et al demonstrated an additional 1% age-related risk of nonchromosomal abnormalities in women age 35 or older.[7] Conversely, Baird et al found no association between the incidence of congenital malformations and advancing maternal age.[8] In fact, more recent studies suggest that young

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maternal age actually may be a stronger risk factor for certain congenital anomalies compared with advanced age.[12–14] Limitations of many of these studies include their reliance on birth certificate data, which is often incomplete and subject to ascertainment bias. Furthermore, the majority of available studies have been unable to capture information on stillbirths and terminations, thereby likely missing a significant proportion of anomalous fetuses. Finally, existing studies largely have been unable to account for the multiple confounders that may independently increase the risk for congenital anomalies.

Given this limited and conflicting data, the objective of this study was to estimate the risk of major congenital anomalies in women of advanced maternal age in the absence of aneuploidy using a large ultrasound and perinatal database. This information will be useful in counseling women about their risk of having a structurally normal fetus, especially in the setting of normal aneuploidy screening.

Materials and Methods

This was a retrospective cohort study of consecutive patients with a singleton gestation presenting to the Division of Ultrasound and Genetics, Washington University in St. Louis for second-trimester anatomic survey from 1990 to 2009. Institutional review board approval from our institution was obtained. All anatomic surveys performed between 16 and 24 weeks gestation were included. If all sonographic views could not be completed during the initial examination, patients were asked to return in 2 to 4 weeks' time for completion of the anatomic survey. Multiple gestations and pregnancies with chromosomal abnormalities were excluded. Chromosomal abnormalities were identified through prenatal diagnosis or postnatal testing, when examination findings were suspicious. Maternal demographic information, obstetrical history, and medical history are routinely obtained through patient questionnaire at each encounter and entered into a comprehensive database. All suspected fetal anomalies and sonographic markers of aneuploidy are also entered into this database at the time of the examination. Ultrasound examinations are performed by dedicated obstetrical sonographers and are interpreted by maternal–fetal medicine specialists. Pregnancy and neonatal outcomes are prospectively collected by a dedicated nurse outcome coordinator. All sonographically suspected fetal anomalies are confirmed after birth. In addition, anomalies diagnosed after birth are also collected and entered into the database by the nurse outcome coordinator. Neonatal information is obtained by medical record abstraction as well as questionnaire or phone call to the patient or referring obstetric provider.

Study groups were defined by maternal age $\leq$ 34 years and maternal age $\geq$ 35 years at the time of delivery.[15] The primary outcome of the study was the presence of one or more major anomalies diagnosed at the time of second trimester ultrasound. This outcome was chosen to capture all anomalous pregnancies, including those that may result in stillbirth or termination. An anomaly was defined as a defect in the structure of an organ which resulted from a specific primary abnormality of organogenesis.[16] Examples of major anomalies include congenital heart defects, neural tube defects, gastroschisis, and omphalocele. Markers of aneuploidy, such as thickened nuchal fold or absent/hypoplastic nasal bone, were not considered to be major congenital anomalies. Secondary outcomes included the distribution of individual major congenital anomalies by organ system, including central nervous system (CNS), cardiac, renal, thoracic, head and neck, musculoskeletal, gastrointestinal, and abdominal wall defects.

Baseline maternal characteristics as well as the incidence of the primary and secondary outcomes were compared between the study groups using chi-square and Fisher exact tests for categorical variables and Student *t*-test for continuous variables. Normality of distribution was assessed using the Kolmogorov–Smirnov test. The distribution of anomaly type by organ system was also compared between the study groups. A Cochran–Armitage test for trend was used to evaluate for any significant pattern in the incidence of major fetal malformations across maternal age categories. Univariable analysis was used to estimate the relative risks (RR) and 95% confidence intervals (CIs) of the association between the AMA and major congenital malformations. Multivariable logistic regression analysis then was used to estimate the adjusted odds ratio (aOR) for the primary and secondary outcomes, controlling for confounders identified both historically and through univariable analysis. Separate logistic regression models were run for each organ system, and nonsignificant variables were removed in a backward stepwise fashion. A subgroup analysis was also performed comparing the risk of major congenital anomalies in women age $\geq$ 40 years and women $\leq$ 39 years. The p values < 0.05 were considered statistically significant. All statistical analysis was performed using STATA 12.0 special edition software (StataCorp, College Station, TX).

Results

A total of 76,453 patients with singleton gestations were included in our perinatal database over the study period. After excluding 297 (0.4%) patients with fetal chromosomal abnormalities, 76,156 patients comprised our final study cohort. Of these patients, 20,803 (27.3%) were AMA. On average, patients who were AMA were of higher gravidity and parity and had a lower body mass index (BMI) compared with patients who were not AMA. Patients who were AMA also were more likely to be Caucasian, report a history of alcohol use during pregnancy and have a history of chronic hypertension and/or diabetes (both preexisting and gestational) (►**Table 1**). Finally, patients who were AMA were significantly more likely to present at an earlier gestational age for second trimester anatomic survey compared with patients $\leq$ 34 years old (18.7 $\pm$ 1.6 weeks vs. 19.4 $\pm$ 1.7 weeks; $p < 0.001$).

The overall incidence of major fetal anomalies in our cohort was 2.4% ($n = 1{,}804$). There was a statistically significant decrease in the incidence of all major congenital anomalies with increasing maternal age until the threshold of age 35 ($p < 0.001$). This incidence ranged from 3.2% in women $<$ 20 years old to 1.7% in women $>$ 35 years old (►**Fig. 1**). ►**Fig. 2** demonstrates the distribution of the major anomalies by organ