Age-specific risk factors for adverse maternal and neonatal outcomes in Xiamen, China: A population-based retrospective study

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Abstract
Background: Elderly mothers are increasingly in China. We are aims to explore whether association between pregnancy to delivery interval and adverse pregnancy outcomes is affected by maternal age. Methods: A population-based retrospective study was performed in Xiamen, China. Data were derived from the Medical Birth Registry of Xiamen from 2011 to 2018. Multivariable logistic regression was used to conduct multivariable analyses based on adjusting the factors to evaluate the effect of maternal age on pregnancy outcomes. Results: Among 77,859 pregnant women with specific age, gestational diabetes mellitus (GDM) risk were increased for women aged 40 years or older (42.9%; aRR, 3.84 (3.26-4.51); P < 0.001), but not for pregnant women aged less than 25 years (9.2%; aRR, 0.60 (0.54-0.68)). Increased cesarean, preterm birth, large-for-gestational age (LGA), and low birth weight risks were more pronounced for pregnant women aged 40 years or older (66.5%, 8.4%, 26.5%, and 6.7%, respectively; aRR, 3.77 (3.14-4.52), 1.26 (0.90-1.79), 1.31 (1.08-1.60), and 1.10 (0.74-1.65), respectively; all P < 0.001). Risk of Apgar < 7 at 5 minutes were increased for women < 25 years old compared with women 35 to 39 years old (0.2% vs. 0.1%; aRR, 2.05 (0.85-4.93) vs. 0.63 (0.14-2.86)). Conclusion: Advanced maternal age increased risk of adverse pregnancy outcomes. The risk ratio of GDM, cesarean, preterm birth, LGA, and low birth weight is higher, which suggests pregnant women should guard against related risk factors and choose an appropriate mode of production. Furthermore, pregnant women should choose an ideal age for pregnancy to make themselves and child healthy.

Background
Pregnancy is a unique period that is defined as high-risk based on the higher risk for adverse pregnancy outcomes compared to general population[1]. Meanwhile, the demographics of childbearing have a significant shift. The data of United States showed pregnant women aged 35 to 39 years increased by 36% between 1991 and 2001, and the incidence among pregnant women aged 40 to 44 years elevated by a significant 70%. Surprisingly, pregnant women aged between 50 and 54 years who born 263 infants in 2002 [2]. Clearly, the advanced maternal age (AMA) has become a trend based on economic and social influences. Today, prolonged education, career priority, fertility
control via effective contraceptive methods, heavy working conditions and economic stress result in postponed pregnancy age [3,4].

AMA is defined as pregnant women get pregnancy aged ³ 35 years. A study showed 14% of all children were born by 35 years and older mothers[5]. Although the question of advantage and disadvantage of AMA has been debated over many years, it is still a divisive conclusion. Many studies have researched the effects of maternal age, which indicated AMA is associated with gestational diabetes mellitus (GDM), cesarean delivery, obesity, hypertension, hyperbilirubinemia, perinatal mortality and maternal morbidity [6]. A UK study performed in 2017 found that compared with young mothers, the children born to mothers older than 35 years revealed better cognitive abilities [7]. As well, older mothers had offspring later presented healthier behaviors during pregnancy [7].

According to these contradictory results and a small number of Chinese related studies, we conducted this study to explore the effects of AMA on mother and children.

Methods

Study population

All pregnant women were registered at community health centers when they get pregnancy. If pregnant women get a 32 gestational week, they will be referred to a higher level hospital for healthcare until delivery. The data of pregnant women were collected from the Medical Birth Registry of Xiamen (MBRX) between January 2011 and March 2018. The MBRX was established in 2007 in China, which included information of all live and stillbirths from 12 gestational weeks that was based on a compulsory policy. The participants information were derived from the MBRX, which was connected by individual information record linking to the Xiamen citizen health information system using the unique identification number of every Xiamen citizen.

Data collection

Baseline data of maternal characteristics at pregnancy and pregnancy outcomes were extracted from MBRX records. The maternal characteristics included maternal age, level of education, parity, pre-pregnancy body mass index (BMI), fasting plasma glucose (FPG), systolic blood pressure (SBP), diastolic blood pressure (DBP), oral glucose tolerance test (OGTT) value, family history of diabetes,
and family history of hypertension. The pregnancy, labor, and delivery characteristics contained gestational weight gain, gestational age at delivery. The information on infants included birth weight, gender, and Apgar score. Furthermore, the pregnancy outcomes contained GDM, caesarean, preterm birth, small-for-gestational age (SGA), large-for-gestational age (LGA), macrosomia, low birth weight, stillbirth, and Apgar < 7 at 5 minutes.

**Definitions**

GDM diagnosis criteria were referred to the 2014 National Health and Family Planning Commission of the People’ Republic of China. Pregnant women would be considered to have GDM if one of the following plasma glucose values was met or exceeded: 0 hour, 5.1mmol/L; 1 hour, 10.0mmol/L; or 2 hours, 8.5mmol/L. Even if the test was performed after 28 weeks, it was still considered valid. LGA was defined as birth weight was above 90 percentile for gestational age, according to gestational age and gender-specific intergrowth-21st curves [8]. SGA referred to birth weight less than the 10th percentile for gestational age. Preterm birth was defined as giving birth earlier than 37 weeks of pregnancy. Low birth weight was defined as birth weight < 2,500g. Macrosomia was diagnosed with birth weight > 4,000g.

**Statistical analysis**

Statistical analysis was performed by SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables was showed as Mean±SD and compared by one-way ANOVA. Discontinuous variables were presented as n (%) and compared by Chi-square (c²) test. Multivariable logistic regression was used to conduct multivariable analyses based on adjusting the factors to evaluate the effect of maternal age on pregnancy outcomes. The variables adjusted for pre-pregnancy BMI, SBP, DBP, FPG, family history of diabetes, parity, and level of education.

**Results**

**Characteristics of study population and maternal age categories**

There are 77,859 pregnant women with specific age who were registered in MBRX March 1, 2011, and March 30, 2018. As showed in Table 1, maternal age was classified into five groups: < 25 years, 25-29 years, 30-34 years, 35-39 years, and ≥ 40 years. We observed that the pre-pregnancy BMI was slightly
increased with age, $P < 0.001$. In contrast, the gestational weight gain was decreased with age, $P < 0.001$. For maternal age ³ 40 years, the SBP (110.82±11.48) and DBP (67.98±8.79) were highest compared with other four groups, all $P < 0.001$. The most population of all groups received more than nine years of compulsory education, $P < 0.001$. More than half of pregnant women under the age of 29 have their first child; most women above the age of 30 years have their second child, all $P < 0.001$. For infants of four groups, more than half are male. Furthermore, we found that OGTT value at 0h, 1h, and 2h all expressed as slightly increasing with age for four groups, all $P < 0.001$.

**Association between pregnancy outcomes and maternal age**

As presented in Table 2, in this study, 13,681, 22,265, 3,317, 2,732, 2,119, 3,221, 2,495, and 75 pregnant women were subjected to GDM, caesarean delivery, preterm birth, SGA, LGA, macrosomia, low birth weight, stillbirth, and Apgar < 7 at 5 minutes, respectively. The incidence of GDM, caesarean delivery, preterm birth, and LGA was 42.9%, 66.5%, 8.4%, and 26.5%, respectively in maternal age ³ 40 years group, which was highest, all $P < 0.001$. For maternal age < 25 years, the proportion of SGA and stillbirth was highest, which was 4.9%, and 4.5%, respectively, all $P < 0.001$.

**Effect of maternal age on adverse pregnancy outcomes**

The association between maternal age and pregnancy outcomes is presented in Table 3. The crude risk ratio (cRR) of GDM was increased with maternal age, the specific cRR as follows: 0.60 for < 25 years; 25-29 years as a reference; 1.77 for 30-34 years; 3.01 for 35-39 years; 4.44 for ³ 40 years; $P < 0.001$. Meanwhile, the adjusted risk ratio (aRR) of GM was also increased with maternal age, $P < 0.001$. Pregnant women who aged < 25 years, 1.86 times more risk for infants to suffer from Apgar < 7 at 5 minutes compared with pregnant women who aged 25-29 years. In addition, we observed that both cRR and aRR of caesarean increased with maternal age, all $P < 0.001$. Women aged ³ 40 years, 4.50 times more risk to select caesarean delivery. As well, the cRR and aRR all elevated with maternal age, all $P < 0.001$. Pregnant women who aged ³ 40 years, 1.89 times more risk to deliver LGA. The risk of preterm birth was also increased with maternal age, all $P < 0.001$. For age ³ 40 years, the cRR of preterm birth reached 1.81 (1.41-2.33). Furthermore, we found that pregnant women who aged > 35 years, 1.47 times more risk for infants to suffer from low birth weight. The RR of low birth weight
increased with maternal age, all $P < 0.001$

Discussion

We observed that the risk of GDM, cesarean delivery, preterm birth, LGA, and low birth weight increased with maternal age. Furthermore, AMA increased the risks of low Apgar < 7 at 5 minutes. In this study, GDM was more frequent in the AMA group, which is consistent with most studies [9-11]. A meta-analysis indicated AMA women who aged 35-40 years and > 40 years were more likely to have GDM[12]. However, a study revealed that no significant difference was observed between AMA and chronic disease-GDM [13]. Some studies elucidated that the cause of AMA is risk factor for GDM was due to insulin sensitivity and pancreatic b-cell function fall with maternal age [14,15]. Furthermore, some studies only included low risk pregnant women still indicated similar results in the AMA women [15,16].

High risk of cesarean delivery increased with maternal age for non-medical reasons [17]. Large study [18] showed that after adjusting for variables about maternal characteristics, the cesarean rate was still higher, which suggesting AMA might be a risk factor for cesarean delivery. A hypothesizing biological mechanism for high risk of cesarean delivery reported that longer duration and poor progression of labour with advanced age, impairment of myometrial contractility and dystocia are the most frequently discussed causes. [18,19] Although cesarean delivery is a safe intervention, it still remains an invasive surgical procedure with intrinsic adverse influences for pregnant women. It is suggested that the benefit-risk balance should be taken into account when mother choosing the mode of delivery [20].

Our study found that AMA is a risk factor for preterm birth over the full gestational age range, especially aged ≥ 40 years, which was consistent with other study [21]. Firstly, the intrauterine infection was a cause of preterm birth has been reported [22]. Secondly, hormonal disorders-progesterone deficiency- is another factor, which is significant for pregnancy maintenance, and concentrations decrease with maternal age[23]. Thirdly, emotional stress can also play a key role in causal pathway [24]. Last but not least, AMA may lead to the myometrial and placental vascular lesions related to preterm birth [25]. A study expressed SGA and pre-eclampsia increased with
maternal age, and these conditions are related with vascular disorders [26].

Furthermore, our study indicated the risk of low birth weight still increased with maternal age. Some studies showed no differences in birth weight among different age [27,28]. The association between AMA and low birth weight is seldom affected by education level and socioeconomic factors [28,29]. Several researches reported both premature delivery and poor placental perfusion can lead to low birth weight. [15,30] Interestingly, the risk of Apgar < 7 at 5 minutes reduced with maternal age. Whereas, a study indicated the AMA women were more likely to suffer from worse Apgar scores [12]. Another study revealed the incidences of 5-minute Apgar scores of 7 was not affected by maternal age [31]. These outcomes vary greatly, possibly due to different sample sizes.

The major strengthen of this study is large sample sizes. Meanwhile, there are also some limitations. Firstly, this study is an observational nature results in we cannot exclude the presence of a possible unmeasured residual confounding. Another limitation is the high proportions of missing values for history of preterm birth; nevertheless, the outcomes were consistent with the complete analysis. Furthermore, the population of this study was Chinese, which may limit the external validity the results for other countries or ethnicity.

Conclusions
Our study found that AMA is a risk factor for GDM, cesarean delivery, preterm birth, LGA, and low birth weight. It is suggested that pregnant women should choose an ideal age for pregnancy to make themselves and child healthy. Furthermore, the young maternal age is a risk for Apgar < 7 at 5 minutes, which is different from other studies. Therefore, further researches are needed to identify these results in other populations, and to declare the underlying biological mechanisms. Additionally, understanding causes is significant for the design of public health policy and interventions.

Abbreviations
AMA, advanced maternal age; GDM, gestational diabetes mellitus; LGA, large-for-gestational age;
SGA, small-for-gestational age; BMI, body mass index; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure

Declarations
Ethics approval and consent to participate This is a retrospective cohort study that did not require
informed consent, which was approved by the ethics committee of the First Affiliated Hospital of Xiamen University that composed and worked in accordance with the Chinese GCP and relevant regulations. The application number was KYH2018-007. In addition, this study was carried out in accordance with the rules of the Declaration of Helsinki of 1975, revised in 2013.

*Consent for publication* Not application.

*Availability of data and materials* All data are held by Xiamen Diabetes Institute. It is available on request from Xiamen Diabetes Institute.

*Competing interests* The authors declare that they have no competing interests.

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*Author’s contribution* C Y-L and H L-L collected and analyzed data, wrote the first draft, and created the table. S W-J and L F-P designed the statistical method and directed statistical analyses of the data. C Z, H B-K, and W L-Y analyzed and interpreted the data. S H-Q and L X-J designed the study, and revised the submission. All authors contributed to the discussion, and approved the final manuscript.

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Tables

Table 1 Maternal and infant characteristics by maternal age categories among study population
## Maternal characteristics

|                          | < 25 years | 25-29 years | 30-34 years | 35-39 years | > 40 years | P value |
|--------------------------|------------|-------------|-------------|-------------|------------|---------|
| Mean age, years          | 22.90±1.2  | 26.99±1.3   | 31.57±1.3   | 36.49±1.3   | 41.04±1.3  | < 0.001 |
| Pre-pregnancy BMI, kg/m² | 20.28±2.6  | 20.68±2.7   | 21.56±2.8   | 22.36±2.8   | 22.66±2.7  | < 0.001 |
| Gestational weight gain, kg | 13.91±4.0 | 13.61±4.0   | 12.38±4.3   | 10.97±3.9   | 10.56±4.6  | < 0.001 |
| Fasting plasma glucose, mmol/L | 4.64±0.44 | 4.69±0.46   | 4.73±0.47   | 4.79±0.49   | 4.83±0.49  | < 0.001 |
| Systolic blood pressure, mmHg | 107.22±10.56 | 107.56±10.69 | 107.90±10.69 | 108.79±11.02 | 110.82±11.48 | < 0.001 |
| Diastolic blood pressure, mmHg | 65.06±7.8 | 65.76±7.7   | 66.01±8.0   | 66.60±8.2   | 67.98±8.7  | < 0.001 |
| Level of education, n (%) |            |             |             |             |            |         |
| £ 9 years                | 2228 (38.3) | 3871 (17.9) | 2355 (21.5) | 982 (29.7)  | 173 (34.6) | < 0.001 |
| > 9 years                | 3596 (61.7) | 17742 (82.1) | 8579 (78.5) | 2329 (70.3) | 327 (65.4) | < 0.001 |
| Parity, n (%)            |            |             |             |             |            |         |
| 1                        | 3995 (66.4) | 13025 (58.6) | 3389 (30.5) | 442 (13.1)  | 42 (8.3)   | < 0.001 |
| 2                        | 2019 (33.6) | 9202 (41.4)  | 7708 (69.5) | 2927 (86.9) | 467 (91.7) | < 0.001 |
| Family history of diabetes, n (%) | 70 (1.1) | 470 (2.0)  | 371 (3.2)  | 140 (4.0)   | 22 (4.2)   | < 0.001 |
| Family history of hypertension, n (%) | 158 (2.4) | 958 (4.1)  | 729 (6.3)  | 314 (9.0)   | 51 (9.8)   | < 0.001 |
| OGGT at 24-28 weeks, mmol/L |            |             |             |             |            |         |
| Fasting plasma glucose   | 4.40±0.36  | 4.46±0.37   | 4.54±0.40   | 4.61±0.41   | 4.70±0.54  | < 0.001 |
| 1 h                      | 7.25±1.55  | 7.75±1.61   | 8.18±1.66   | 8.62±1.69   | 8.93±1.79  | < 0.001 |
| 2 h                      | 6.22±1.18  | 6.60±1.30   | 7.00±1.41   | 7.40±1.50   | 7.81±1.71  | < 0.001 |
| Birth outcomes           |            |             |             |             |            |         |
| Birth weight, kg         | 3.20±0.43  | 3.22±0.47   | 3.23±0.46   | 3.22±0.49   | 3.23±0.50  | < 0.001 |
| Gestational age at birth, weeks | 39.01±1.4 | 38.91±1.4  | 38.66±1.5  | 38.40±1.6  | 38.29±1.5  | < 0.001 |
| Infant sex, male, n (%)  | 3643 (52.1) | 13085 (53.3) | 6678 (53.7) | 2097 (53.5) | 349 (57.0) | 0.075  |

### Table 2: Association between pregnancy outcomes and maternal age

| Pregnancy outcomes | < 25 years | 25-29 years | 30-34 years | 35-39 years | > 40 years | P value |
|--------------------|------------|-------------|-------------|-------------|------------|---------|
| GDM                | 1111 (9.2) | 5715 (14.5) | 4375 (23.1) | 2054 (33.7) | 426 (42.9) | < 0.001 |
| Caesarean birth    | 2297 (23.5)| 9857 (30.7) | 6801 (42.6) | 2763 (53.8) | 547 (66.5) | < 0.001 |
| Preterm birth      | 430 (4.5)  | 1502 (4.8)  | 918 (5.9)   | 399 (7.9)   | 68 (8.4)   | < 0.001 |
| SGA                | 467 (4.9)  | 1431 (4.6)  | 614 (3.9)   | 193 (3.8)   | 27 (3.3)   | < 0.001 |
| LGA                | 1315 (13.8)| 5011 (16.0)| 3252 (20.8) | 1203 (23.8) | 215 (26.5) | < 0.001 |
| Macrosoma          | 279 (2.9)  | 1041 (3.2)  | 561 (3.5)   | 209 (4.1)   | 29 (3.5)   | 0.001   |
| Low birth weight   | 461 (4.7)  | 1499 (4.7)  | 861 (5.4)   | 345 (6.7)   | 55 (6.7)   | < 0.001 |
| Stillbirth         | 434 (4.5)  | 1317 (4.2)  | 568 (3.6)   | 156 (3.1)   | 20 (2.5)   | < 0.001 |
| Apgar < 7 at 5 minutes | 17 (0.2)   | 30 (0.1)    | 22 (0.1)    | 6 (0.1)     | -          | 0.217   |
Table 3 Association between pregnancy outcomes and maternal age categories

| Maternal age, years | GDM† | Caesarean | SGA        | LGA        | Macrosomia |
|---------------------|------|-----------|------------|------------|------------|
| < 25                | cRR  | 0.60 (0.56, 0.64) | 0.70 (0.66, 0.73) | 1.07 (0.96, 1.19) | 0.84 (0.78, 0.89) | 0.88 (0.78, 1.00) |
|                     | aRR  | 0.60 (0.54, 0.68) | 0.67 (0.62, 0.72) | 0.90 (0.77, 1.05) | 0.97 (0.89, 1.07) | 1.08 (0.89, 1.30) |
| 25-29               | cRR  | 1 | 1 | 1 | 1 | 1 |
|                     | aRR  | 1 | 1 | 1 | 1 | 1 |
| 30-34               | cRR  | 1.77 (1.70, 1.85) | 1.68 (1.62, 1.75) | 0.85 (0.77, 0.94) | 1.38 (1.31, 1.45) | 1.09 (0.98, 1.21) |
|                     | aRR  | 1.67 (1.57, 1.78) | 1.54 (1.46, 1.63) | 1.00 (0.88, 1.14) | 1.12 (1.05, 1.20) | 0.89 (0.77, 1.03) |
| 35-39               | cRR  | 3.01 (2.83, 3.19) | 2.63 (2.48, 2.79) | 0.83 (0.71, 0.96) | 1.63 (1.52, 1.75) | 1.27 (1.09, 1.47) |
|                     | aRR  | 2.49 (2.29, 2.70) | 2.10 (1.94, 2.27) | 0.99 (0.80, 1.23) | 1.14 (1.04, 1.26) | 0.88 (0.72, 1.08) |
| ≥ 40                | cRR  | 4.44 (3.91, 5.05) | 4.50 (3.88, 5.21) | 0.72 (0.49, 1.06) | 1.89 (1.61, 2.21) | 1.09 (0.75, 1.59) |
|                     | aRR  | 3.84 (3.26, 4.51) | 3.77 (3.14, 4.52) | 0.92 (0.56, 1.50) | 1.31 (1.08, 1.60) | 0.84 (0.54, 1.30) |
| P value for trend   | cRR  | < 0.001 | < 0.001 | 0.733 | < 0.001 | 0.288 |
|                     | aRR  | < 0.001 | < 0.001 | 0.733 | < 0.001 | 0.288 |

GDM, gestational diabetes mellitus; SGA, small-for-gestational age; LGA, large-for-gestational age.
cRR, crude risk ratio; aRR, adjusted risk ratio. † aRR adjusted variables for pre-pregnancy BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, and family history of diabetes in five groups. Other aRR adjusted variables for pre-pregnancy BMI, systolic blood pressure, diastolic blood pressure, parity, and level of education.