Preconception glucose level mediates the effect of advanced maternal age on offspring birthweight:a population-based cohort study

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Abstract

Objective: To investigate the mediation effect of glucose level on the linking between maternal age and offspring birthweight. Design: Cohort study Setting: Single tertiary center Population: Women who participated in the National Free Preconception Health Examination Project from January 2015 to September 2017 in Dongguan city, China. Methods: A causal mediation analysis was applied to test the potential mediation effect of the glucose level on the association between maternal age and offspring birthweight. Main Outcome Measure: Offspring weight, macorosmia Results: Of 12 044 women with singleton birth were included. The mean birthweight was 3163.12 ± 417.20 g, the frequency of macrosomia was 1.9%, and 1.8% women were in a hyperglycemic state. Mothers aged 30 years and over were significantly more likely to have preconception hyperglycemia [OR (95% CI): 1.82 (1.31, 2.52)]. Both maternal age and preconception glucose level had a significant positive linear association with macrosomia after adjusted potential confounding factors [OR (95% CI): 1.66 (1.22, 2.26), 1.30 (1.14, 1.47), respectively]. The mediation analysis showed that the presence of preconception glucose level mediated significantly 8% [95% CI: 4% to 16%] of the total influence of maternal age on offspring birthweight. Additionally, the mediated effect was increased among women with a history of adverse pregnancy by mediating 18%. Conclusion: The preconception glucose level mediated the association of advanced maternal age with offspring birthweight. It suggested that the importance of preconception glycemic monitoring and control among older mothers to reduce the risk of adverse pregnancy outcome.

INTRODUCTION

Delaying motherhood is reported worldwide with the usage of assisted reproductive technologies, high education level and successful career in women (1-3). In China, with universal two child policy (announced in October 2015), the numbers of mother aged 35 and over have increased obviously (4). Previous studies have reported that advanced maternal age had a high risk of adverse obstetrical and perinatal outcomes (5). The tendency of advanced childbearing age draws our attention to the worse outcomes of the offspring in this particular risk group, trying to find the underlying mechanism.

Fetal macrosomia is defined as birthweight $>$ 4000g, which is a crucial pregnancy outcome because of the maternal and neonatal adverse outcomes subsequently (6). The risk factors for fetal macrosomia include genetic, environmental and metabolic disorders (7). And one of the intriguing findings was that advanced maternal age was an independent predictor for macrosomia(8, 9). Comorbidities during pregnancy and reproductive aging may to some extent contribute to the poor pregnancy outcome of advanced maternal age (10-12). However, in older pregnant women irrespective of comorbidities there are still worse obstetric outcomes (13, 14). There remains unknown on mechanism why advanced maternal age has greater offspring birthweight.

On the other hand, previous studies found that advanced maternal age was significantly more likely to be diagnosed with diabetes mellitus or hyperglycemia during pregnancy (15-17), suggesting that the older pregnant

women might have higher glucose level. Moreover, high glucose level before, during, and after pregnancy, is related to abnormal offspring birthweight (18-21). Notably, the preconception glucose level is recognised as the indicator of gestational diabetes (22). And it plays an important role in the preconception care to reduce the risk of the worse pregnancy outcome, since that hyperglycemia during pregnancy couldn't be well controlled (23). Recently, Yumei Wei et.al reported the linear association between preconception fasting plasma glucose (FPG) level and macrosomia (24), suggesting that preconception glucose level initially affected offspring birthweight. Thus, it indirectly suggests that high glucose level before pregnancy might initially contribute potentially to the association between advanced maternal age and macrosomia. We assumed that preconception FPG level mediated the association between advanced maternal age and offspring birthweight, which prior studies have not been able to account for this.

Using prospective data from a population-based cohort study, we assessed preconception FPG level in advanced versus non-advanced pregnant women, investigating the association between maternal age and macrosomia. Furthermore, we studied for the first time the contribution of preconception FPG level to the effect of advanced maternal age on offspring birthweight by a mediation analysis.

Materials and methods

Participants

We recruited reproductive-age women who participated in National Free Preconception Health Examination Project (NFPHEP) from January 2015 to September 2017 in Dongguan of Guangdong province of China. The details of the NFPHEP were described elsewhere (25). Briefly, women intended pregnancy within six months, were provided with free preconception examinations by well-trained health workers, including a standardized questionnaire and laboratory examinations. Then, the subsequent pregnancy outcomes of women (number of fetus, infant outcome, birthweight, gestation, date of delivery, etc.) were follow-up from medical records. Basic information included demographic characteristics (maternal age, nation, levels of education, height, weight, BMI, etc.), lifestyle (history of passive smoking, work condition of exposure to radiation/heat/organic solvent/heavy metal/ pesticides/other toxic substances etc.), history of choric disease (diabetes, hypertension, thyroid disease, heart disease, anemia), reproductive history (spontaneous/induced abortion, stillbirth, pregnancy, parity, etc.). In strict accordance with National Guide to Clinical Laboratory Procedures, serum FPG level of women was detected by glucose oxidase or hexokinase methods in the local laboratories, and accepted the external quality assessment and quality control biannually (26).

This study was approved by the Ethical Committee of Maternal and Children Health Care Hospital of Donguan City. The informed consents were obtained from each participant.

Variables

Birthweight was collected by medical records. Fetal macrosomia was defined as birthweight [?]4000 g. Maternal age was defined at the time of preconception examinations. Maternal age was either as continuous or as categorical variable. According to the result of association between maternal age and macrosomia by cubic restricted splines (as shown in Figure 1a), above 30 years old was regarded as "advanced maternal age". Hyperglycemia was defined as FPG levels $>$ 5.6mmol/L, with no self-reported diabetes mellitus.

Statistical Analysis

Mean (standard deviation) and frequency (percentage), respectively, described the continuous and categorical variables. Baseline characteristics were compared by maternal age group using Student's t-test for continuous variables and Pearson's Chi-squared test for categorical variables. The potential confounding factors included BMI, nation, levels of education, history of passive smoking, work condition, history of adverse pregnancy outcomes (including stillbirth, spontaneous and induced abortion), parity, which were adjusted by following multivariate regressions. The associations between maternal age and hyperglycemia/macrosomia were assessed with multivariate logistic regression model by adjusted the potential confounding factors. Odds ratio (OR) and 95% confidence interval (95%CI) were estimated. We also conducted cubic restricted splines fitted

in a logistic regression model with knots at the 5th, 35th, 65th, and 95th percentiles, to probe the association between macrosomia and maternal age / FPG (continuous variable). Furthermore, a causal mediation analysis using the mediation package in R software (27) was performed to explore the potential contribute of preconception FPG level to the effect of advanced maternal age on offspring birthweight , with 1000 Monte Carlo draws. Average causal mediation effects (ACMEs), average direct effects (ADEs), total effects (sum of a mediation effect and a direct effect), and the percentage of the variability in the total causal effect explained by the mediator were showed. Findings at$p$ <0.05 were considered significant. Statistical analyses were performed using R-3.6.1 software.

RESULTS

In this study, we finally included eligible 12 044 reproductive-age women with singleton birth. We excluded 5414 women without successful pregnancy within six months. Women who had a singleton birth were eligible for this study (N = 13 380). Participants with history of chronic disease and stillbirth were excluded, yielding an analytic sample of 12 044 women (Figure 1).

The median of time from baseline examination to pregnancy was 2.2 months (interquartile range (IQR):1.07-3.67). The mean maternal age was 29.16 ± 4.73 years old, and 17.18 % was aged 30 and over. The mean birthweight was 3163.12 ± 417.20 g, and the frequency of macrosomia was 1.9%. In terms of maternal FPG level before pregnancy, 1.8% women were in a hyperglycemic state. Around 17.5% women had a history of adverse pregnancy outcomes. Most of the women were Han (99.3%) and college or higher (77.2%). The percentage of history of passive smoking and parity over three times were 31.1 and 17.1, respectively.

Table 1 showed the baseline characteristics of study subjects according to maternal age. Compared with younger mothers, women with advanced age were more likely to be greater birthweight and higher preconception FPG levels. And, the frequency of macrosomia and hyperglycemia was significantly increased among older mothers. Women with advanced age showed to be higher BMI and college or higher, had more history of adverse pregnancy outcomes and parity.

In adjusted logistic regression model (Table 2), maternal age and BMI was associated with hyperglycemia. Women with advanced age significantly had a higher adjusted OR for hyperglycemia by 1.82 (95% CI, 1.31 to 2.52). Every one unit increased in BMI was associated with a 4% increase per 1 kg/m^2 in the risk of hyperglycemia (OR: 1.04; 95% CI: 1.02 to 1.06).

When maternal age was modeled as a continuous variable and fitted in the multivariate logistic regression model using cubic restricted splines, continuously increasing trend was found between maternal age and macrosomia (Figure 2a, P $_{\text{linear}}$< 0.001). It showed that the age of 30 years were likely to be reasonable cutoff values for advanced maternal age regarding the macrosomia. Similarly, an obvious linear association was also observed for preconception FPG levels in macrosomia (Figure 2b, $P_{\text{linear}} < 0.001$). Based on this age cutoff values, in multivariate logistic regression model, women with advanced age had a significant increase of macrosomia (OR: 1.66; 95% CI: 1.22 to 2.26, Table 3). Similarly, a positive association was found between the risk of macrosomia and preconception FPG level before pregnancy (**OR** : 1.30; 95% CI: 1.14 to 1.47, Table 3).

Finally, we explored the contribution of preconception FPG levels to the association of advanced maternal age with offspring birthweight by a causal mediation analysis (Table 4). Overall, the total influence of maternal age on offspring birthweight (the β coefficient), which includes independent and mediated effects, was 4.89 (95% CI: 2.92 to 6.81). The presence of preconception FPG level mediated significantly 8% (95%CI: 4% to 16%) of the total influence of advanced maternal age on offspring birthweight. Additionally, the mediated effect was increased among women with history of adverse pregnancy outcomes by mediating 18%.

DISCUSSION

To our knowledge, this is the first study to explore the mediating effect of glucose level on the linking between advanced maternal age and offspring birthweight. We found the positive linear association between maternal age and macrosomia, and the total influence of maternal age on offspring birthweight was mediated 4% to

16% by preconception FPG level, which was more obvious among women with a history of adverse pregnancy outcomes (mediating 18%).

We confirmed that maternal age had a linear association with the risk of macrosomia, which was in line with most previous studies (28, 29). We noticed that a majority of studies defined various cutoff values of advanced maternal age taking all the adverse pregnancy outcomes into consideration, such as 35 or 40 years old (30, 31). In view of macrosomia, we firstly applied cubic restricted splines and found that the age of 30 years would be the reasonable cutoff value for advanced maternal age, which was consistent with Xiaolei's definition with the join point regression (32).And, based on the cutoff value, women with advanced age would have a 66% increase in the risk of macrosomia.

We identified that the underlying pathway of the influence of advanced maternal age on offspring birthweight involved the preconception FPG level. Advanced maternal age was associated with higher preconception FPG level, which was consistent with the prior result that preconception diabetes mellitus had advanced age (24). E Cosson et.al proposed that the preconception hyperglycemia indicated the FPG was already increased during early pregnancy and might persist in late-pregnancy while insulin resistance increased (20), resulting the increasing risk for macrosomia (19). Salman et.al also reported that the pre-pregnancy impaired fasting glucose level was associated with increased risk for gestation diabetes mellitus (33), which indicating the mediating effect of glucose level might be persistent during pregnancy. Our study supported those prior results and confirmed the real relationship among preconception FPG level, maternal age and offspring birthweight. Notably, although the proportion of macrosomia among older reproductive-age women was low, the total effect would be large with the increasing number of delaying motherhood in China and the worse prognosis of macrosomia. In addition, it's a challenge to monitor glucose level for women during pregnancy (34, 35), and the glycemic control before pregnancy among this risk group would be implication.

Interestingly, we further found that the mediating effect of glucose level was more obvious among older women with a history of adverse pregnancy outcomes. In our study, 94.2% adverse pregnancy outcomes were spontaneous and induced abortion. It was reported spontaneous abortion could increase the prevalence of insulin resistance, which resulting in the glucose intolerance and increasing the transport of glucose (36, 37). Similarly, induced abortion associated with metabolic syndrome such as glucose intolerance in women with age [?] 40 years (38). Glucose intolerance in older women with a history of adverse pregnancy outcomes might to some extent explained the increased mediated effect of glucose level on birthweight of advanced maternal age. Our finding suggested that we should pay more attention to the preconception glycemic control before pregnancy for older women with a history of adverse pregnancy outcomes.

There are some limitations in our study. First, the 2-hour plasma glucose level and HbA1c concentration were not detected. Second, we did not get access to the glucose level during pregnancy. However, this may not change the mediating effect of glucose level since that the high glucose level indicated the increasing glucose level during early pregnancy (20). Third, the glycemic control status among reproductive-age women was unknown, which may underestimate the risk (24). Finally, the dietary patterns were not available, further study need to be explored.

CONCLUSION

In conclusion, we demonstrated the mediating role of the preconception glucose level in the association between advanced maternal age on offspring birthweight (mediating 8%), especially among women with a history of adverse pregnancy outcomes by mediating 18%. These results suggested the importance of preconception glycemic screening and control for older reproductive-age women to reduce the adverse pregnancy outcomes.

Disclosure of interests

None declared.

Contribution to authorship

Bi Jiang, Meixia Wang, and Xinjian Zhang were involved in the conception of the project. Bi Jiang, Weichao He, Jingyun Yu, Sishi Wei, and Xinjian Zhang were involved in the planning of the study. Bi Jiang, Meixia Wang, Sishi Wei, Weichao He, and Jingyun Yu were involved in data collection and carrying out the study. Bi Jiang, Meixia Wang, and Xinjian Zhang were involved in the analysis of the project. Bi Jiang, and Meixia Wang primarily wrote the manuscript, with editing and contributions from all authors.

Details of ethics approval

This study was approved by the Ethical Committee of Maternal and Children Health Care Hospital of Donguan City: 2019(14), 31 October 2019.

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Table 1. Baseline Characteristics of Study Subjects According to Maternal Age	**Table 1.** Baseline Characteristics of Stu
Variables	< 30
Birth Weight (mean (SD))	3135.92 (404.98)
Macrosomia	
No	6880 (98.6)
Yes	101 (1.4)
FPG level	4.54 (0.59)
Hyperglycemia	
No	6844 (98.8)
Yes	85 (1.2)
BMI (mean (SD))	20.16 (3.93)
Nation	
Han	6938 (99.4)
Others	43 (0.6)
Levels of Education	
College or higher	5104 (77.4)
Junior high school or below	243 (3.7)
Senior high school or Secondary	1244 (18.9)
History of Passive Smoking	

No	4597 (67.4)
Yes	2220 (32.6)
Work Condition	
No	6197 (91.4)
Yes	586 (8.6)
History of Adverse Pregnancy Outcomes	
No	6303 (90.3)
Yes	678 (9.7)
Parity	
<3	6648 (95.2)
3	333 (4.8)

Table 3. Associations between Maternal Age/FPG level and Macrosomia

Variables
Maternal Age
< 30
30
FPG level

NOTE: a, univariate analysis; b, adjusted by BMI, nation, levels of education, history of passive smoking, work condition, h

Table 3. Associations between Maternal Age/FPG level and Macrosomia

Variables
Maternal Age
< 30
30
FPG level

NOTE: a, univariate analysis; b, adjusted by BMI, nation, levels of education, history of passive smoking, work condition, h

Table 4. Causal Mediation Analysis of Direct and Indirect Influences of Preconception FPG level in the relationship between Maternal Age and Offspring Birthweight	**Table 4.** Causal Mediation Analysis of Direct and Indirect Influences of Preconception FPG level in the relationship between Maternal Age and Offspring Birthweight ACMEs (95% CI)	**Table 4.** Causal Mediation Analysis of Direct and Indirect Influences of Preconception FPG level in the relationship between Maternal Age and Offspring Birthweight ADEs (95% CI)	**Table 4.** Causal Mediation Analysis of Direct and Indirect Influences of Preconception FPG level in the relationship between Maternal Age and Offspring Birthweight Total Effect (95% *CI*)	**Table 4.** Causal Mediation Analysis of Direct and Indirect Influences of Preconception FPG level in the relationship between Maternal Age and Offspring Birthweight Prop.Mediated (95% *CI*)
Overall	0.40 (0.18,0.63)*	4.48 (2.53,6.39)*	4.89 (2.92,6.81)*	0.08 (0.04,0.16)*
Women with Adverse Pregnancy Outcomes History				

	0.78 (0.21,1.47)*	3.09 (-1.54,7.42)	3.87 (-0.72,8.37)$^{++}$	0.18 (-0.9,1.50)$^{++}$
Women without Adverse Pregnancy Outcomes History				
	0.30 (0.07,0.53)$^{+}$	4.8 (2.67,6.85)*	5.10 (2.99,7.08)*	0.06 (0.01,0.13)$^{+}$

NOTE: *: <0.001,+: < 0.05, ++: <0.1; CI = confidence interval; The total effect is the sum of a mediation (indirect) effect and a direct effect. Prop. mediated is the variability explained by the mediator.