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Original Article

Preeclampsia Mediates the Association between Advanced Maternal Age and Adverse Pregnancy Outcomes: A Structural Equation Modeling Approach

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Abstract

Background: Advanced maternal age (AMA) is considered a risk factor associated with preeclampsia and adverse pregnancy outcomes. We aimed to assess the mediating role of preeclampsia between AMA and adverse pregnancy outcomes.

Methods: A sample of 14646 pregnant women from the tertiary hospital of Hubei Province, China, during the years 2011-2017 were included in this study. Pregnant women were divided into 4 groups according to their age at delivery. Mediated effect of preeclampsia with relation to AMA and adverse pregnancy outcomes was measured using structural equation modeling.

Results: Women in the highest age group were significantly associated with preterm delivery [RR 1.37 (95% CI 1.24 - 1.49)] and low birth weight [RR 1.28 (95% CI 1.11 - 1.45)] compared with women in the lowest age group. The indirect effect (mediated effect) of AMA on preterm delivery and low birth weight mediated by preeclampsia was [β 0.053 (95% CI: 0.047, 0.060)], and [β 0.045 (95% CI: 0.038, 0.052)], respectively. The estimated mediation proportion of the effect of AMA due to mediated effect of preeclampsia was (35.5%) for preterm delivery and (23.5%) for low birth weight.

Conclusion: Preeclampsia partially mediates the association between AMA and adverse pregnancy outcomes.

Keywords: Advanced maternal age; Preeclampsia; Adverse pregnancy outcomes; Structural equation modeling

Introduction

Advanced maternal age (AMA), defined as a mother who is 35 years or above at the time of delivery, is considered a significant risk factor associated with adverse pregnancy in both high and low-income countries (1). Maternal age at the time of first neonatal birth has dramatically increased in many countries. In the United States, the birth rate in women of AMA was increased 3% from 2013 to 2014 (2), however, the birth rate in teenager mother has fallen 61% from 1991 (3). The trend toward delayed childbearing is also reported in China. In China, during 2004-2014, the birth rate in women of AMA increased from 8.65% to 17.04%. On the other hand, birth rate

in women of 25-29 years old decreased from 102.44 % to 93.62% (2).

Several previous studies have reported the association between AMA and adverse pregnancy outcomes, specifically; AMA was significantly associated with preterm delivery (PTD) (4-6) and low birth weight (LBW) (7-8) among both primigravida and multipara women (1). AMA is also associated with an increased risk of certain pregnancy complications. In particular, women of AMA have an increased risk of placenta previa, gestational diabetes, pregnancy-induced hypertension and preeclampsia (9).

Preeclampsia (PE) is one of the potential causes of maternal and neonatal mortality and morbidity that affects around 3-8% of all pregnancies. The etiology of PE is still elusive. However, maternal obesity, chronic hypertension, kidney disease, diabetes mellitus, nulliparity and AMA are considered the risk factors associated with PE (9). PE is also a potential risk-factor associated with PTD (10), and LBW (11, 12). Several previous studies have reported the association of AMA with adverse pregnancy outcomes and PE but the mediating effect of PE between AMA and adverse pregnancy outcomes has not been documented (4-9).

To the best of our knowledge, mediating effect of PE between AMA and adverse pregnancy outcomes has not examined before in Hubei, China. Therefore, we aimed to examine the mediating role of PE between AMA and adverse pregnancy outcomes.

Materials and Methods

Study Population

This tertiary hospital-based retrospective study was conducted in the Wuhan University Renmin Hospital, Department of Obstetrics and Gynecology, Hubei, China from Jan 2011 to Mar 2017. All data were collected and documented in obstetrics register by trained nurses during individual medical examination.

The study was approved by the Ethical Review Board of Renmin Hospital (ID: WDRY2019–K034) in accordance with the Declaration of Helsinki.

Inclusion and exclusion criteria

A total of 14646 singleton pregnant women were enrolled. We excluded missing data on maternal age, prepregnancy body weight, neonatal gender and gestational age (13). Pregnant women with twin neonates were also excluded from the analysis of data.

Neonatal Birth Outcomes

The measurement of growth parameters were recorded within 24 h of birth, including birth length and birth weight. Neonatal birth length was measured by a newborn stadiometer. The length was taken from the crown to the soles of the feet using a centimeter scale on the newborn stadiometer. Birth weight was recorded in grams immediately after birth. The electronic infant scales were calibrated using a standard weight to ensure accuracy. The Apgar score of neonates has recorded at 1 and 5 minutes after birth. The neonatal mortality (NM) was recorded after neonatal birth (0-28 d).

Definitions

PE is defined as the onset of high blood pressure (≥140/90 mmHg) and often a significant amount of protein (≥0.3 mg/dL) in urine after 20th weeks of pregnancy. PTD is defined as neonatal birth before 37 completed weeks of pregnancy. LBW is defined as birth weight < 2500g. The ponderal index was determined by weight in gm / (length in cm) ^{3}×100. The ponderal index between 2.5 and 3.0 was considered normal, between 2.0 and 2.5 marginal, and a neonate with ponderal index less than 2.0 was considered as a low ponderal index (LPI). NM is defined as the death of neonate occurs in (0-28 days) after neonatal birth. The neonatal mortality rate (NMR) was determined by a number of neonatal deaths/number of live births×1000.

Definition of Confounding Factors

Cofounding factors were selected based on previous literatures which are associated with both

exposure and neonatal birth outcome. The confounding factors included in this analysis were, prepregnancy body weight (≤ 45 kg and ≥ 91 kg), parity and neonatal gender.

Statistical Analysis

A trend analysis using chi-square test was conducted to compare baseline characteristics using groups of maternal age: Group 1 (≤24 years; n= 2912); Group 2 (25-29 years; n= 4544); Group 3 (30-34 years; n= 3836); Group 4 (≥35 years; n= 3354). Furthermore, multivariate Poisson regression was used to determine relative risk (RR) and 95% confidence intervals (CI) for PTD, NM, LBW and LPI, for each group of maternal age. All analyses were adjusted by prepregnancy body weight, parity and neonatal gender.

After finding the association between AMA and adverse pregnancy outcomes, a mediation analysis was conducted using structural equation modeling/ pathway analysis (SEM) approach to test and estimate the total effect, direct effect and indirect effect (mediated by PE) of AMA on PTD and LBW. The total effect, direct effect and indirect effect were computed and analyzed and the mediation proportion was calculated using the formula $\{STD^{DE}(STD^{IE} - 1)/ STD^{DE} * STD^{IE} - 1)\}*100$ (14). In order to evaluate the best fitting model for data, we used different Goodness-of-Fit indices such as Chi-square test, GFI, RMR, RMSEA, CFI and TLI (15). We calculated the coefficients (β) with 95% CI for the total, direct and indirect effects and also estimated the proportion of association mediated by PE. The analyses were performed by SPSS Amos for window version 22 (IBM Corporation, Chicago, USA). *P* <0.05 was taken statistically significant.

Results

Our analysis consisted of 14646 women; among these women, 2912 (19.8 %) were ≤24 years of age and 3354 (22.9%) were older than 35 years of age. About, 417 (2.8%) women were experienced preeclampsia. Around, 2450 (16.7 %) women delivered preterm birth; 2006 (13.6 %) and 620 (4.2 %) women delivered neonates with LBW and LPI, respectively. The NMR was 11.9 /1000 live birth neonates. Women of AMA had significantly higher prevalence of PE, placenta previa, gestational diabetes mellitus and adverse pregnancy outcomes such as PTD, LBW, LPI and NM compared with reference age group (Table 1).

Table 1: Distribution of maternal and neonatal characteristics by age groups (n=14646)

Maternal and neonatal characteristics		*Groups (G) of maternal age*								
		G1(n= 2912) ≤24 years		*G2 (n=4544) 25-29 years*		*G3 (n=3836) 30-34 years*		*G4 (n=3354) ≥35 years*		*P-value*
		No.	%	No.	%	No.	%	No.	%	
Preeclampsia		67	2.3	118	2.6	111	2.9	121	3.6	0.000
Placenta previa		43	1.5	77	1.7	84	2.2	87	2.6	0.000
GDM		38	1.3	127	2.8	176	4.6	241	7.2	0.000
Diabetes		3	0.1	13	0.3	27	0.7	16	0.5	0.003
Cesarean section		1152	39.5	2155	47.4	2275	59.3	2247	67	0.002
Multiparity		302	10.4	695	15.3	1469	38.3	2160	64.4	0.000
Preterm delivery		315	10.8	650	14.3	654	17.1	831	24.7	0.000
Neonatal mortality		19	0.6	39	0.8	51	1.3	66	1.9	0.000
LBW		225	7.7	495	10.8	611	15.9	675	20.1	0.000
LPI		75	2.5	165	3.6	185	4.8	195	5.8	0.000
Low Apgar score		93	3.2	141	3.1	157	4.1	208	6.2	0.000
Neonatal Sex	Male	7996	54.6	7689	52.5	8026	54.8	8143	55.6	0.02
	Female	6650	45.4	6957	47.5	6620	45.2	6503	44.4	

Note: G1 (≤24 years), Group2 (25-29 years), G3 (30-34 years), G4 (≥35 years), GDM, (Gestational diabetes mellitus), LBW (Low birth weight), LPI (Low ponderal index), p-values were calculated using chi-square test

In the adjusted Poisson regression model, increasing maternal age was significantly associated with adverse pregnancy outcomes. Women in the highest age group were significantly associated with PTD [RR 1.37 (95% CI: 1.24, 1.49)] and LBW [RR 1.28 (95% CI: 1.11, 1.45)], but not significantly associated with NM [RR 1.31 (95% CI: 0.82, 1.80)] and LPI [RR 1.27 (95% CI: 0.92, 1.62)] compared with reference age group. Furthermore, women in the age group of (30-34 years) were also significantly associated with PTD [RR 1.20 (95% CI: 1.08, 1.32)] and LBW [RR 1.15 (95% CI: 1.01, 1.31)] compared with reference age group (Table 2).

Table 2: Maternal age and adverse pregnancy outcomes

Maternal age groups	*PTD [RR (95% CI)]*	*NM [RR (95% CI)]*	*LBW [RR (95% CI)]*	*LPI [RR (95% CI)]*
G1	Reference	Reference	Reference	Reference
G2	1.04 (0.93,1.16)	1.07 (0.62,1.51)	1.09 (0.94,1.24)	1.05 (0.74, 1.36)
G3	1.20 (1.08, 1.32)	1.21 (0.76, 1.66)	1.15 (1.01,1.31)	1.13 (0.82, 1.47)
G4	1.37 (1.24, 1.49)	1.31 (0.82, 1.80)	1.28 (1.11, 1.45)	1.27 (0.92, 1.62)

Maternal age groups were as follows: G1 (≤24 years), G2 (25-29 years), G3 (30-34 years), G4 (≥35 years). PTD (Preterm delivery), NM (Neonatal mortality), LBW (Low birth weight), LPI (Low ponderal index). Adjusted for prepregnancy body weight, parity, and neonatal gender

From SEM (Fig. 1), we found that indirect effect (mediated effect) of AMA on PTD and LBW mediated by PE was [β 0.053 (95% CI: 0.047, 0.060)], and [β 0.045 (95% CI: 0.038, 0.052)], respectively. The estimated mediation proportion of the effect of AMA due to an indirect effect mediated though increased risk of PE was largest for PTD (35.5%) followed by LBW (23.5%) (Table 3).

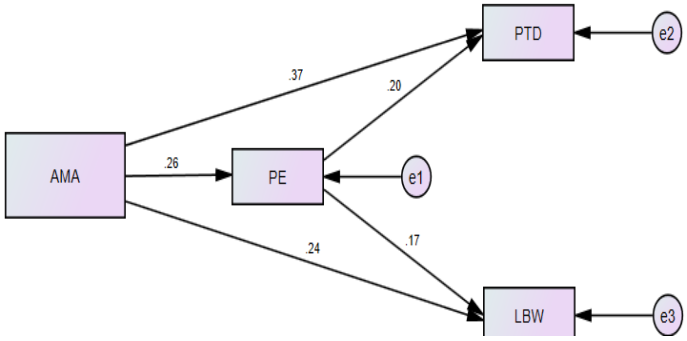

Fig. 1: SEM for AMA, PTD, and LBW using PE is a mediator

Table 3: Direct, indirect and total effect of advanced maternal age on adverse pregnancy outcomes mediated by preeclampsia using structural equation model

Outcomes	*STD direct effect [β (95% CI)]*	*STD indirect effect [β (95% CI)]*	*STD total effect [β (95% CI)]*	*% Mediated*
PTD	0.369 (0.350, 0.388)	0.053 (0.047, 0.060)	0.423 (0.405, 0.440)	35.5%
LBW	0.243 (0.221, 0.265)	0.045 (0.038, 0.052)	0.288 (0.267, 0.308)	23.5 %

Model fit indices; $\chi 2$ test=0.001, GFI=0.93, RMR=0.012, RMSEA=0.000, CFI=0.94, TLI=0.96. STD (Standardized), PTD (Preterm delivery) LBW (Low birth weight). Adjusted for prepregnancy body weight, parity, and neonatal gender

Discussion

In China, pregnancy at AMA is on increasing trend. We reported a tertiary hospital-based adverse pregnancy outcomes in women of aged (30-34 years) and at aged 35 or over at the time of delivery. Our findings suggest that after adjusting of confounder factors, women of AMA and even women (30-34 years) of age were significantly associated with adverse pregnancy outcomes. We found that increased risk of PE partially mediates the association between AMA and adverse pregnancy outcomes. AMA was an independent risk factor associated with PTD. This robust association between AMA and PTD has also been reported in various population-based studies (4, 10). Another two Sweden population-based cohort studies conducted in different regions found that AMA was associated with an increased risk of PTD, irrespective of parity, adjusted for demographic characteristic, smoking and other medical complications (5, 6). The underlying reasons are still remain elusive. One of the reasons may be placental vascular pathology. In fact, spontaneous PTD has been associated with four-to-seven fold increased risk of placental vascular pathology (16). Progesterone deficiency may be another possible factor in the pathway of PTD in older women. The levels of progesterone hormone decrease with increasing maternal age. Low levels of progesterone are associated with PTD and its supplementation was found effective in preventing PTD (17).

We also examined whether AMA was an independently associated with increased risk of LBW. We observed that AMA was a significant risk factor associated with LBW which has also been reported across different population (7, 8). The findings of increased risk of LBW in women of AMA also replicate results on the association between AMA and increased risk of LBW that have been observed in Brazil (18) and Thailand (19). Some previous studies also found the significant association between AMA and increased risk of LBW, which is consistent with our results (6, 20). However, young mothers of 13-19 years old were more significantly associated with increased risk of LBW, compared to mothers of 20-45 years old (21, 22). Two physiological factors such as PTD and hypo-placental perfusion/ preeclampsia may be considered to result in LBW in women of AMA (23).

Our findings depicted that women of aged (30-34 years) were also significantly associated with increased risk of PTD and LBW. In this study, women of aged (30-34 years) had comparatively higher prevalence of PE, placenta previa and gestational diabetes compared to the reference group. Several previous studies had reported the inverse association between PE (24, 25) placenta previa (26), gestational diabetes mellitus (27) and adverse pregnancy outcomes. It suggests that adverse pregnancy outcomes in women of aged (30-34 years) may be because of higher prevalence of PE, placenta previa and gestational diabetes mellitus. Women (30-34 years) of age were significantly associated with increased risk of PTD and other adverse pregnancy outcomes (28). In another population-based register study, increased risk of PTD in women of aged (30-34 years) was found (5). However, no association between women of aged (30-34 years) and adverse pregnancy outcomes were reported (7). These differences in findings could be related to the different definition of AMA. For investigating effects of maternal aging on adverse pregnancy outcomes, the cutoff value for age groups and the definition of the reference group is very crucial. If, for example, women of ≥35 years old are compared with women less than 35 y of age, the effect of maternal aging could be underestimated because of the U-shaped distribution of the adverse pregnancy outcomes (28).

This is the first study to suggest that PE partially mediates the association between AMA and adverse pregnancy outcomes. AMA is associated with increased risk of PE (10, 9), and PE play a significant role in adverse pregnancy outcomes (10, 23). In patients with PE, the utero-placental blood perfusion drops to 50-60 % after 3 to 4 weeks of the complication, and the hypo-utero-placental flow cause insufficient transport of the nutrients (29). It is intuitive that hypo-

uteroplacental blood flow should induce decreased fetal growth, with an increased risk of PTD and LBW (10, 23). We observed that the mediated effect of AMA on PTD (35.5%) was higher than LBW (23.5%). These findings suggest that PE mediates the association between AMA and PTD more robust compared to LBW neonatal outcome.

We acknowledge that our study had certain limitations. Our data analysis was limited to a single centre, which is the potential selection bias in this study. Moreover, our mediation analysis would be subject to an unmeasured confounding, a confounder that has an effect on both the mediator and outcomes of interest. Our study was also lack of collected information related to still birth, smoking and alcohol drinking habits. The study was conducted in only one tertiary hospital. So, our results cannot be generalized to the whole population. We had not enough sample size of the population, which may affect the strength of our results.

Conclusion

AMA and women of aged (30-34 years) were significantly associated with adverse pregnancy outcomes such as, PTD and LBW. Women of AMA had also higher prevalence of PE. PE partially mediates the association between AMA and adverse pregnancy outcomes. Although, AMA are the significant risk factor associated with adverse pregnancy outcomes, but the mediating role of PE between AMA and adverse pregnancy outcomes could not be ignored. Since, our study had not large sample size, therefore, future studies should be encouraged to replicate our findings in other population with large sample size.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

All the authors declare no conflict of interest.

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