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Original Article

Do Hypertensive Disorders of Pregnancy and Abnormal Placentation Mediate the Association between Advanced Maternal Age and Adverse Perinatal Outcomes?

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Abstract

Background: A tertiary-hospital-based retrospective study (2011-2019) was conducted to determine the mediating role of hypertensive disorders of pregnancy and abnormal placentations between advanced maternal age and adverse neonatal outcomes.

Methods: Data from a tertiary-hospital-based retrospective study (n= 23051) was used and conducted regression-based mediation analysis to assess the mediating role of hypertensive disorders of pregnancy and abnormal placentation between the advanced maternal age and adverse neonatal outcomes.

Results: After adjusting for confounding factors, the indirect effect of advanced maternal age on preterm births, perinatal mortality, and low birth weight mediated by hypertensive disorders of pregnancy was [aOR 4.95 (95% CI: 4.05, 5.85)], [aOR 2.82 (95% CI: 1.78, 3.86)], and [aOR 5.90 (95% CI: 4.93, 6.87)], respectively. The indirect effect of advanced maternal age on preterm births and low birth weight mediated by abnormal placentation was [aOR 6.83 (95% CI: 5.70, 7.97)] and [aOR 4.18 (95% CI: 3.26, 5.11)]. About, 23%, 37%, and 17% of the effect of advanced maternal age on preterm births, perinatal mortality, and low birth weight was mediated by hypertensive disorders of pregnancy, respectively. Furthermore, abnormal placentation mediates the association between advanced maternal age and preterm births by 18% and low birth weight by 23%.

Conclusion: Hypertensive disorders of pregnancy and abnormal placentation partially mediate the association between advanced maternal age and adverse neonatal outcomes.

Keywords: Advanced maternal age; Hypertensive disorders of pregnancy; Abnormal placentation; Adverse perinatal outcomes

Introduction

Advanced maternal age (AMA) is defined as a mother of 35 years or older at the time of delivery. Due to the advancement of modern societies, availing of higher education, career development, and economic independence more young girls are likely to delay childbearing until or beyond 30 years of age (1, 2). The birth rate in women with AMA has increased by 96.9% (from 8.65% to 17.04%) during 2004-014, in China. On the other hand, the birth rate in women 25-29 years old decreased from 102.44 % to 93.62% (3).

The AMA has been considered a significant risk factor associated with adverse pregnancy outcomes (4). Women with AMA are significantly associated with hypertensive disorders of pregnancy (HDP), abnormal placenta placentation, and adverse perinatal outcomes (3, 5-7). Specific complications of pregnancy that commonly occur in women with AMA may lead to adverse perinatal outcomes. For example, HDP is common among women with AMA (8) considered one of the significant risk factors for adverse perinatal outcomes (9, 10). Additionally, some evidence suggests that abnormal placentation, another common pregnancy complication among women with AMA (11), is associated with adverse perinatal outcomes (12, 13). Women with abnormal placentation experienced a 5-fold increase in preterm births and perinatal deaths compared with normal women (12). Placental abruption is associated with an 8.9-fold increased risk of stillbirths and 3.9-time with preterm births compared with women without this condition (14).

These findings suggest a potential mechanism linking AMA with adverse perinatal outcomes, but there is a lack of research to explore the possible mediating role of HDP and abnormal placentation in the pathway of AMA and increased risk of adverse perinatal outcomes. Therefore, we aimed to examine the extent to which HDP and abnormal placentation mediate the association between AMA and adverse perinatal outcomes in Hubei, China.

Material and Methods

Study population

A tertiary-hospital-based retrospective study (2011-2019) was conducted in the Wuhan University Renmin Hospital, Department of Obstetrics and Gynecology, Hubei, China.

The study protocol 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 23051 singleton pregnant women were selected for the study. We excluded missing data on maternal age, pre-pregnancy body weight, neonatal gender, birth weight, birth length, and gestational age (15). Pregnant women of aged ≤18 years old, with chronic hypertension, and twin neonates were also excluded from the analysis of data.

Collection of data on maternal traits

Data regarding maternal traits were collected from the obstetrics register including maternal age, parity, prepregnancy body weight, gestational age, education, occupation, and pregnancy complications. At the time of delivery, based on age, pregnant women were divided into two groups (i) <35 years, (ii) and ≥35 years. Gestational age was calculated by the date of the last known menstrual period and confirmed by ultrasound examination during the first and second trimester.

Definition of exposures and perinatal birth outcomes

Pregnancy hypertension (PH) is defined as having blood pressure greater than 140/90 mmHg without proteinuria after 20th weeks of gestation (16). Preeclampsia (PE) is defined as elevated blood pressure 140/90 mmHg with proteinuria (albumin > 0.3g in 24 hours) after the 20th week of gestation (17). Sever PE referred to having a blood pressure higher than 160/110 mmHg with proteinuria (al-

bumin > 5g in 24 hours) after the 20th week of gestation (18). Placenta previa is defined as suboptimal placental implantation near or over the cervical opening (19). Placental abruption referred to the early separation of the placenta before childbirth (20). Preterm birth is defined as a neonate born before 37 completed weeks or fewer than 259 days from the first date of a woman's last menstrual period (21). Perinatal mortality is defined as the combination of late fetal mortality (stillbirths) and early neonatal mortality (0-6 days of life) (22). Fetal macrosomia defined is as birth weight ≥4000g and low birth weight (LBW) is defined as birth weight < 2500g (23). Intrauterine growth restriction (IUGR) is defined as a condition of fetal growth that is below the 10th percentile for its gestational age and does not reach its genetically predetermined growth potential (24). Apgar score was recorded at 1 minute, and at 5 minutes after birth. Apgar score was divided into two categories (i) low Apgar score (<7), and (ii) normal Apgar score (≥ 7) (25). 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 a ponderal index less than 2.0 was considered a low ponderal index (LPI) (26). Congenital defects are defined as abnormalities in the structure of neonatal body parts that occur during intrauterine development (27).

Predictor Variable

In mediation analysis, AMA was taken as a predictor variable for adverse perinatal outcomes. AMA was taken as a dichotomous (1 if AMA ≥35 years, 0 otherwise)

Outcomes Variable

Adverse perinatal outcomes (i.e. preterm births, LBW, and perinatal mortality) were taken outcomes variable in our mediation analysis. Adverse perinatal outcomes were dichotomous (1 if preterm births, 0 otherwise, and so on).

Potential mediators

HPD (composite of PH, PE, and severe PE), and abnormal placentation (composite of placenta previa and placental abruption) were potential mediators in the analysis. These mediators were dichotomous (1 if HDP, 0 otherwise, and so on).

Potential confounding factors

The confounding factors included in this analysis were, maternal education, occupation, pre-pregnancy body weight (≤ 45 kg and ≥ 91 kg), parity, and neonatal gender.

Statistical analysis

We used regression-based mediation analysis. In this analysis, the major focus is to determine how an intermediated variable (mediator/M) mediates the effect of the predictor variable (PV) on an outcome variable (OV) (28). Hence, the M lies on the causal pathway between the PV and the OV as shown in Fig. 1. This regression-based mediation analysis consisted ofF four steps. In Step 1, AMA (X) predicts adverse perinatal outcomes (Y) to test for path c (i.e. $Y= B_0 +B_1X+e$). In step 2, AMA (X) predicts mediator (M) to test for path a (i.e. $M= B_0 +B_1X+e$). In step 3, mediator (M) predicts adverse perinatal outcomes (Y) to test for path b (i.e. $Y= B_0 +B_1M+e$). In step 4, AMA (X) and mediator (M) both predict adverse perinatal outcomes (Y) to test for path c' (i.e. $Y= B_0 +B_1X+B_2M+e$). In general, if one or more steps from step 1 to step 3 are non-significant, then researchers usually conclude that mediation is not possible. Furthermore, in step 4, if X is no longer significant when M is controlled, then it is called full mediation. However, if X is still significant and both X and M significantly predict Y, the finding supports partial mediation (29). The hallmark of this regression-based mediation approach is that confounding variables and covariates can be included in the models.

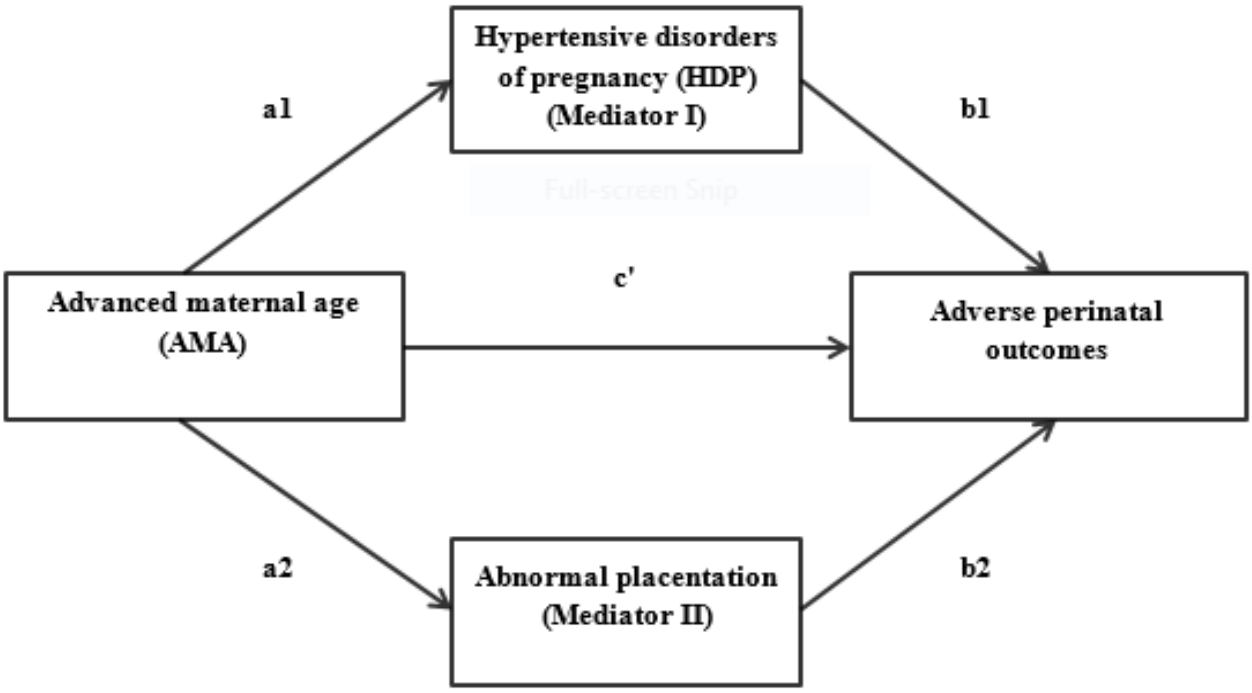

Fig. 1: Indirect effect of advanced maternal age (AMA) on adverse perinatal outcomes through HDP (Mediator I) and abnormal placentation (Mediator II)

According to the Baron and Kenny statistical mediation approach (29), the total effect (TE) of the PV on the OV is the sum of indirect effect or mediated effect (ME) and direct effect (DE). The ME is the effect of the PV on OV mediated by the M, whereas the DE is the effect of the PV on OV keeping the M constant. The ME was estimated by multiplying the regression coefficient of the effect of PV on M from Model 2 (path a) with the regression coefficient of the effect of M on the OV from Model 3 (path b) (29, 30). One of the best ways of expressing ME is by determining the "mediation proportion (MP) or % mediation," which is the proportion of the TE explained by a particular M (30, 31). The MP was determined by a theoretical model as 1- C'/C proposed by Baron and Kenny (29). Whereas (c) represents the TE (sum of DE and ME) of PV on OV and c' represents the ME of PV on OV with M included as a covariate, which is obtained from (Models 1, 2, 3 & 4). $P<0.05$ was taken statistically significant. The data were analyzed by using SPSS (Statistical Package for Social Sciences) for window version 22 (IBM Corp., Armonk, NY, USA).

Results

Our analysis consisted of 23051 singleton pregnant women. Among these women, 82.8% were less than 35 years of age and 17.2% were with AMA. Women with AMA had a significantly higher prevalence of PH, PE, severe PE, placenta previa, preterm births, perinatal mortality, and LBW compared with women aged less than 35 years (Table 1).

The adjusted odds ratios (aOR) and p-value from mediation regression analysis are shown in Table 2-4. The estimated mediation proportion among AMA, preterm births, perinatal mortality, and LBW accounting for possible mediation by HDP was 23%, 37%, and 17%, respectively (Table 5).

Table 1: General maternal-neonatal characteristics and pregnancy outcomes by maternal age groups (N=23051)

Maternal characteristics and pregnancy complications	*Groups of maternal age*				*P-value*
	<35 years (n=19095)		≥35 years (n=3956)		
	No.	%	No.	%	
Primiparous (≤1)	15167	(79.4)	2316	(58.5)	0.001
Multiparous (>1)	3928	(20.6)	1640	(41.5)	0.001
C- section*	11084	(58.0)	2922	(73.8)	0.001
Previous history of C-section*	2486	(13.0)	1107	(28.0)	0.001
HDP					
PH*	218	(1.1)	65	(1.6)	0.01
PE*	855	(4.5)	261	(6.5)	0.001
Severe PE*	99	(0.5)	35	(0.8)	0.006
Abnormal placentation					
Placenta previa*	718	(3.8)	247	(6.2)	0.001
Placental abruption*	42	(0.2)	12	(0.3)	0.3
GDM*	1108	(5.8)	430	(10.8)	0.001
Diabetes*	81	(0.4)	20	(0.5)	0.5
Neonatal characteristics and outcomes					
Preterm birth*	3399	(17.8)	1013	(25.6)	0.001
Perinatal mortality*	238	(1.2)	90	(2.3)	0.001
LBW*	2574	(13.5)	697	(17.6)	0.001
IUGR*	145	(0.8)	23	(0.6)	0.2
LPI*	729	(3.8)	166	(4.2)	0.2
Low Apgar score*	656	(3.4)	182	(4.6)	0.001
Fetal distress*	432	(2.3)	89	(2.2)	0.9
Macrosomia*	1035	(5.4)	217	(5.5)	0.8
Congenital defects*[a]	244	(1.3)	54	(1.4)	0.6
Neonatal gender					
Male	10148	(53.1)	2177	(55)	0.03
Female	8947	(46.9)	1779	(45)	

Note: *= Frequency and percentage of variables with only 'Yes' value presented**,** [a]Congenital defects (microtia, anotia, polydactyly, heart defects, limb reduction defects, cleft lip, cleft palate, and hydrocephaly), p-*values* were calculated using chi-square test

Table 2: Mediation regression analysis of HDP and abnormal placentation between AMA and preterm births

Models and variables	*aOR*	*95%CI*	*p-value*
HDP (M 1)			
Model 1			
AMA	1.56	1.34 – 1.58	0.001
Model 2			
AMA	1.51	1.32 – 1.71	0.001
Model 3			
HDP	3.28	2.93 – 3.66	0.001
Model 4			
AMA	1.41	1.31 – 2.54	0.001
HDP	3.01	2.72 – 3.39	0.001
Abnormal placentation (M 2)			
Model 1			
AMA	1.56	1.34 – 1.58	0.001
Model 2			
AMA	1.49	1.29 – 1.73	0.001
Model 3			
Abnormal placentation	4.59	4.01 – 5.22	0.001
Model 4			
AMA	1.42	1.31 – 1.54	0.001
Abnormal placentation	4.51	3.97 – 5.14	0.001

Note: M1 and M2 (mediator 1 and mediator 2, respectively)

Table 3: Mediation regression analysis of HDP and abnormal placentation between AMA and perinatal mortality

Models and variables	*aOR*	*95%CI*	*P-value*
HDP (M 1)			
Model 1			
AMA	1.71	1.32 – 2.18	0.001
Model 2			
AMA	1.51	1.32 – 1.71	0.001
Model 3			
HDP	1.87	1.33 – 2.64	0.001
Model 4			
AMA	1.66	1.29 – 2.14	0.001
HDP	1.81	1.28 – 2.55	0.001
Abnormal placentation (M 2)			
Model 1			
AMA	1.71	1.32 – 2.18	0.001
Model 2			
AMA	1.49	129 – 1.73	0.001
Model 3			
Abnormal placentation	1.47	0.95 – 2.28	0.082
Model 4			
AMA	1.68	1.31 – 2.17	0.001
Abnormal placentation	1.42	0.91 – 2.20	0.12

Note: M1 and M2 (mediator 1 and mediator 2, respectively)

Table 4: Mediation regression analysis of HDP and abnormal placentation between AMA and low birth weight

Models and variables	*aOR*	*95%CI*	*p-value*
HDP (M 1)			
Model 1			
AMA	1.28	1.16 – 1.41	0.001
Model 2			
AMA	1.51	1.32 – 1.71	0.001
Model 3			
HDP	3.91	3.48 – 4.37	0.001
Model 4			
AMA	1.22	1.11 – 1.34	0.001
HDP	3.85	3.44 – 4.32	0.001
Abnormal placentation (M 2)			
Model 1			
AMA	1.28	1.16 – 1.41	0.001
Model 2			
AMA	1.49	129 – 1.73	0.001
Model 3			
Abnormal placentation	2.81	2.45 – 3.23	0.001
Model 4			
AMA	1.25	1.13 – 1.37	0.001
Abnormal placentation	2.77	2.41 – 3.19	0.001

Note: M1 and M2 (mediator 1 and mediator 2, respectively)

Table 5: Direct, indirect, and total effect of AMA on adverse perinatal outcomes mediated by HDP and abnormal placentation

Outcomes	*Direct effect [aOR (95%CI)]*	*Indirect effect [aOR (95%CI)]*	*Total effect [aOR (95%CI)]*	*%Mediated*
M 1				
Preterm births	1.56 (1.34, 1.58)	4.95 (4.05, 5.85)	6.51 (5.39, 7.43)	23
Perinatal mortality	1.71 (1.32, 2.18)	2.82 (1.78, 3.86)	4.53 (3.10, 6.04)	37
LBW	1.28 (1.16, 1.41)	5.90 (4.93, 6.87)	7.18 (6.09, 8.28)	17
M 2				
Preterm births	1.56 (1.34, 1.58)	6.83 (5.70, 7.97)	8.39 (7.04, 9.55)	18
LBW	1.28 (1.16, 1.41)	4.18 (3.26, 5.11)	5.46 (4.42, 6.52)	23

Note: M1 and M2 (mediator 1 and mediator 2, respectively).

Discussion

AMA is a potential risk factor for HDP, abnormal placentation, and adverse perinatal outcomes. Moreover, HDP and abnormal placentations are also potential causes of adverse perinatal outcomes (preterm births, perinatal mortality, and LBW). Consistent with our results, several previous studies have reported the association of AMA with HDP, abnormal placentation, and adverse perinatal outcomes, but to our knowledge, the mediating role of HDP, abnormal placentation between AMA, and adverse perinatal outcomes has not been documented in the prior published research (4-8). In the present study, we observed that HDP and abnormal placentation partially mediate the association between AMA and adverse perinatal outcomes.

PE partially mediates the association between AMA, preterm births, and LBW (32). PE mediated the association between AMA and preterm births by 35.5% and 23.5% between AMA and LBW (32). However, some studies found different mediators which mediate the association between maternal risk factors and adverse perinatal outcomes. For example, preterm births and IUGR together mediated the association between lower maternal education and infant mortality by 55% and 60% between medium maternal education and infant mortality compared with high maternal education. Moreover, preterm births and IUGR separately mediated the relationship between lower maternal education (46% and 11%), medium maternal education (48% and 13%), and infant mortality, respectively (33).

Gestational age partially mediated the association between congenital heart defect and reduced neonatal birth weight and the mediation proportion was 40.7% (33). Mendola et al. (34) observed the mediating role of preterm births in the relationship between PE and neonatal health outcomes. They suggested that PE was associated with many neonatal complications through pathways not mediated by preterm births but, maybe due to the anti-angiogenic factors. Preterm births mediate the association between placental abruption and perinatal mortality (35). The proportion mediation through preterm births between placental abruption and perinatal mortality was 28.1%. These studies observed (33-36) the mediating role of preterm births in the association between maternal factors and neonatal outcomes. However, in our study, we did not limit our analysis to term neonates to eliminate the possible mediating effect of preterm births which might be a sequential mediator between AMA, pregnancy complications (HDP and abnormal placentation), and adverse perinatal outcomes (perinatal mortality and LBW). In our findings, the percent (%) mediation was higher for perinatal mortality (37%) than preterm births (23%) when HDP was taken as a mediator. Similarly, the estimated mediation proportion for LBW (23%) was higher than preterm births (18%) when abnormal placentation was considered as a

mediator. The higher percent mediation for perinatal mortality and LBW suggests that in addition to HDP and abnormal placentation, there is also a substantial impact of preterm births on perinatal mortality and LBW (37, 38). This further confirms that preterm births could also play a sequential mediator in the pathway of AMA and adverse perinatal outcomes (perinatal mortality and LBW) as observed between maternal malaria and perinatal mortality (39). These findings improve our understating of underlying pathways between AMA and adverse perinatal outcomes, which should be taken into consideration during designing preventive strategies. Interventional strategies should focus on improving health in women of AMA to reduce the risk of HDP and abnormal placentation which may help to prevent adverse perinatal outcomes.

Our data analysis was limited to a single center, which is the potential selection bias in this study. We used the conventional mediation analysis method and the mediation analysis would be subject to unmeasured confounding, a confounder that has an effect on both the mediator and outcomes of interest. The mediators (HDP and abnormal placentation) were taken as composite variables due to small size data and couldn't find the individual mediating role between AMA and adverse perinatal outcomes.

Conclusion

HDP and abnormal placentation partially mediate the association between AMA and adverse perinatal outcomes. Moreover, as we have shown that HDP and abnormal placentation play a significant role in mediating the effect of AMA on adverse perinatal outcomes, but there is might be other undiscovered pathways implicated in these associations.

Journalism Ethics 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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