

Advanced Maternal Age, Gestational Diabetes, and Parity: A Moderated Mediation Model for Preeclampsia

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Abstract

Background: As the trend of delaying pregnancy continues to grow globally, the prevalence of preeclampsia is expected to increase along with it, placing a significant burden on health systems. This study explores the mediating roles played by gestational diabetes and parity in the relationship between maternal age and preeclampsia.

Methods: This retrospective study considered 700 full-term pregnancies, with preeclampsia being the outcome of interest. Data were gathered from pregnant women at the El Idrissi provincial hospital in Kenitra, Morocco. We used Hayes' PROCESS macro model 7 (version 4.2) to analyze the direct effects and indirect effects in terms of moderated mediation while controlling for any family history of hypertension and hyperglycemia.

Result: The results show that gestational diabetes partially mediates the relationship between maternal age and preeclampsia with an indirect effect of 0.5275 (Boot SE = 0.2833, Boot CI%: 0.0151, 1.1258) for patients of advanced age and 0.8824 (Boot CI %: 0.0266, 1.7895) for those of very advanced age. In addition, parity moderates this relationship (advanced age x parity: $\beta=0.2339$, 95% CI: 0.1372, 0.3306; very advanced age x parity: $\beta=0.2446$, 95% CI: 0.0343, 0.4549). Finally, the mediating effect of gestational diabetes is also moderated by parity with a moderated mediation index of 0.4964 (Boot CI %: 0.0103, 1.1143) for patients of an advanced age and 0.5192 (Boot SE = 0.3677, Boot CI %: 0.0005, 1.4035) for those of a very advanced age.

Conclusion: A very advanced maternal age is an independent risk factor for preeclampsia. Multiparous women, especially older women, also have an increased risk of gestational diabetes, further increasing the risk of preeclampsia.

Keywords: maternal age; gestational diabetes; preeclampsia; parity; moderated mediation model.

Introduction

According to the International Federation of Gynecology and Obstetrics (FIGO), an advanced maternal age (AMA) is defined as being 35 years or older at the time of the expected delivery (Frick, 2021). This age limit was historically established based on the reduced fertility and increased risk of chromosomal abnormalities and miscarriages that typically occur after this age (Lopian et al., 2023). Currently, the definition of very advanced maternal age (vAMA) is a matter of some debate, although some researchers consider an age of 40 years or more at the time of expected delivery to be a very advanced maternal age (vAMA) (Kahveci et al., 2018).

Delaying pregnancy until an older age carries significant health risks for women and their babies because women aged over 35 years at the time of delivery exhibit increased rates of gestational diabetes (Vounzoulaki et al., 2020), preeclampsia (Vandekerckhove et al., 2021), and

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maternal and neonatal morbidity and mortality (Vounzoulaki et al., 2020). Moreover, these risks increase further with increasing maternal age.

As the trend of delaying pregnancy continues to grow globally, the prevalence of preeclampsia is expected to increase along with it, placing a significant burden on health systems. Nevertheless, many of the complications associated with preeclampsia are preventable, highlighting the importance of closely monitoring pregnant women and making timely interventions to optimize maternal and neonatal outcomes.

International research has recently indicated that the proportion of AMA and vAMA pregnant women is increasing year by year (J. Cao et al., 2022). In addition, with the spread of assisted reproduction techniques, the proportion of AMA mothers is expected to increase over the years to come (Shan et al., 2018). According to a survey conducted by the World Health Organization (WHO) among 308,149 mothers and newborns in 29 countries in Africa, Asia, Latin America and the Middle East, the proportion of AMA mothers reached 12.3% (Laopaiboon et al., 2014).

Recent studies have also shown that advanced maternal age and gestational diabetes are significant predictors of preeclampsia (Dai et al., 2023; J. Li et al., 2023; Sun et al., 2023). Additionally, a large-scale meta-analysis of 120 million participants revealed a near-universal trend, namely that the risk of gestational diabetes (GDM) increases linearly with age (Y. Li et al., 2020). Preeclampsia has also been significantly associated with gestational diabetes (J. Li et al., 2023). Nevertheless, the exact biological mechanisms linking maternal age, GDM, and preeclampsia are only partially understood, although many pregnancy-related conditions involve changes in oxidative stress and inflammation (Al-Gubory et al., 2010; Mullins et al., 2013; Myatt & Cui, 2004).

These alterations have also been observed with ageing, so they could affect placental function in older women (Barja, 2014; de Steenwinkel et al., 2013; Girard et al., 2014; Myatt, 2010; Schetter et al., 2010). Indeed, studies have identified placental dysfunctions in older women, such as reduced amino acid transport, abnormalities in cell turnover, and reduced placental efficiency (Lean et al., 2017). The precise association between maternal age and GDM remains unclear, although elevated insulin resistance, increased levels of circulating adipokines and inflammatory markers, and oxidative stress may at least partially explain this phenomenon (Fontana et al., 2007; Shin & Song, 2015).

He et al. also proposed the hypothesis that there is a reduced concentration of fatty acids in the placenta of women aged 35 and older, with this being accompanied by elevated inflammatory markers like IL-1 β and TNF- α in the context of GDM (He et al., 2022). However, the specific signalling pathway that could explain the connection between lipid metabolism and glucose homeostasis in the context of GDM remains unclear.

Nevertheless, gestational diabetes contributes to preeclampsia through hyperglycemia, inflammation, neutrophil hyperactivation, and oxidative stress, because these factors impair placental vascularization, thus triggering preeclampsia, and obesity only amplifies these mechanisms (Yang & Wu, 2022).

Given the significant associations among an advanced maternal age, preeclampsia, and gestational diabetes, as well as the association between gestational diabetes and preeclampsia, it is plausible that gestational diabetes plays a mediating role in the relationship between an advanced maternal age and preeclampsia. Nevertheless, few studies have examined how advanced maternal age and gestational diabetes interact to worsen preeclampsia outcomes.

The interaction between parity and age on the risk of gestational diabetes also modifies the effect of age on this risk during pregnancy. According to Dai et al. advanced age and parity increase the risks of both gestational diabetes and preeclampsia, with their interaction intensifying the risks (Dai et al., 2023). Thus, multiparity (i.e., the second or further pregnancy) together with advanced maternal age may exacerbate the negative effect of gestational diabetes in causing preeclampsia. Our study examines and tests these links through a moderated mediation model.

The proposed conceptual model is presented in Figure 1. Based on a literature review, we formulated the following hypotheses:

Hypothesis 1. Gestational diabetes mediates the relationship between maternal age and preeclampsia.

Hypothesis 2. Parity moderates the relationship between maternal age and gestational diabetes.

Hypothesis 3. Parity moderates the mediating effect of gestational diabetes on the relationship between maternal age and preeclampsia.

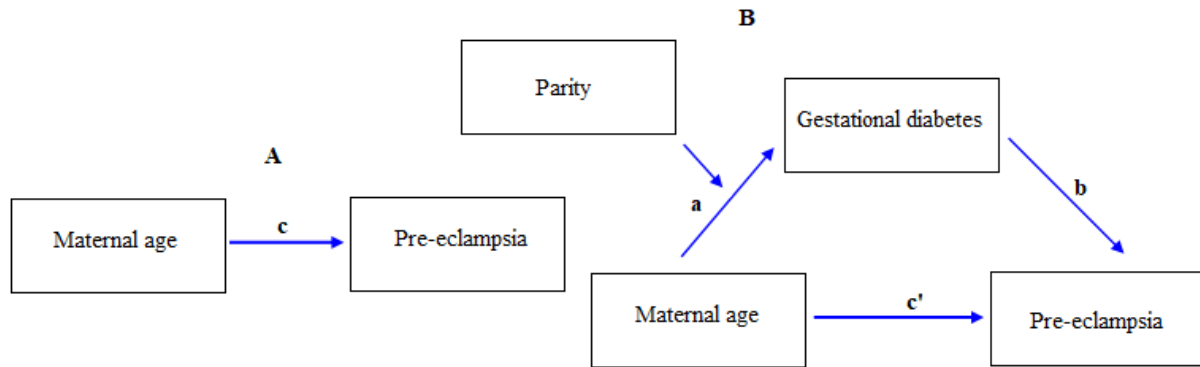


Figure 1: The hypothesized mediating effect of gestational diabetes on the association between advanced maternal age and preeclampsia and the proposed moderating effect of parity. (A) depicts the direct effect of maternal age on pre-eclampsia, while (B) depicts how the effect of maternal age on pre-eclampsia is mediated by gestational diabetes. Interaction index a refers to the direct effect of the predictor on the mediator, b refers to the direct effect of the mediator on the outcome variable, c refers to the direct effect of the predictor on the outcome, and c' refers to the direct effect of a predictor after controlling for the indirect effect of the predictor through the mediator on the outcome.

Materials and Methods

The Study Population and Research Design

This study was conducted in Kénitra Province in the Rabat-Salé-Kénitra region in the northwest of Morocco. This province had approximately 1,061,435 inhabitants in 2015, and it is divided between urban areas (606,993 inhabitants) and rural areas (454,442 inhabitants). There are approximately 214,640 households, including 139,687 in urban areas and 74,953 in rural areas (HCP, 2015).

This retrospective study was conducted at the maternity ward of El Idrissi Provincial Hospital in Kenitra, Morocco between April and October 2021. It collected information by reviewing patient records at this tertiary hospital for 700 pregnant women who attended prenatal consultations in primary health centres and gave birth at this maternity ward.

During this empirical study, we took into account three types of bias to guarantee reliable results. Selection bias was reduced through representative random sampling (Infante-Rivard & Cusson, 2018). For classification bias (Greenland, 1980), we checked the classification of subjects to avoid errors linked to exposure and the risks being studied (i.e., gestational diabetes and preeclampsia). In addition, multivariate logistic modelling was used to account for potential confounding factors (Jean et al., 2009).

Exposure

According to the International Federation of Gynecology and Obstetrics (FIGO), an advanced maternal age (AMA) is defined as being 35 years or older at the time of expected delivery (Frick, 2021). This age limit was determined in the past based on the reduced fertility and increased risks of chromosomal abnormalities and miscarriages that typically occur after this age (Lopian et al.,

2023). For this study, the term “very advanced maternal age” (vAMA) refers to women expected to give birth at the age of 40 or older (Lean et al., 2017).

Outcome

Preeclampsia is associated with significant proteinuria (greater than 0.3 g per 24 hours) and pregnancy-related hypertension (i.e., systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than 90 mmHg) manifesting after the 20th week of amenorrhea (Fox et al., 2019).

The Mediating Role of Gestational Diabetes

This study considered gestational diabetes as a mediator of interest in the relationship between maternal age and the risk of preeclampsia. This variable was selected based on previous studies that have demonstrated its association with maternal age (Schummers et al., 2018) and preeclampsia (J. Li et al., 2023).

A fasting capillary blood glucose test was performed at the first prenatal visit (fasting positive ≥ 0.92 and ≤ 1.25 g/l). The women were invited again at a gestational age between 24 and 28 weeks to fast for an induced hyperglycemia test (OGTT) with 75g of glucose (positive fasting ≥ 0.92 g/l or after 1 hour ≥ 1.8 g/l or after 2h ≥ 1.53 g/l) (Utz & Assarag, 2016).

The Moderating Effect of Parity

Parity, which can be divided into primiparous and multiparous, can play a significant role in increasing the risk of gestational diabetes in older women (Dai et al., 2023; Orazulike et al., 2015). Women with an older maternal age and multiparity have an increased risk of gestational diabetes (Wagan et al., 2021). These findings suggest that parity may act as a buffer against the negative consequences of an advanced maternal age. In particular, if gestational diabetes mediates the relationship between maternal age and preeclampsia, and parity modifies the relationship between maternal age and gestational diabetes, then the mediating effect of gestational diabetes should also be influenced by parity.

Covariates

Confounding factors connected to maternal age, preeclampsia, and gestational diabetes were considered as potential covariates (Endeshaw et al., 2016; Lamminpää et al., 2012; Lewandowska, 2021; Sun et al., 2023). A family history of hypertension (yes or no) and a family history of hyperglycemia (yes or no) were considered to be potential confounders in this study.

Ethical Considerations

This investigation followed the ethical principles of the Declaration of Helsinki for medical research involving human subjects. The necessary authorizations were obtained from the Regional Directorate of the Ministry of Health in Rabat and from the Directorate of the El Idrissi provincial hospital to gain access to maternity services that were needed to conduct the study. The participants also gave oral consent before any interviews where applicable.

Data Analysis

All analyses were performed using SPSS and Stata, version 18. The continuous variables are expressed as mean \pm standard deviation. Student's *t*-test was adopted to compare two groups of variables. However, the parametric ANOVA test and multiple comparisons of means by Bonferroni's test were used to estimate the significance of differences between the parameters examined.

Following the procedure of Baron and Kenny, we examined the mediating effect of gestational diabetes on the relationship between maternal age and preeclampsia (Baron & Kenny, 1986) (Figure 1).

A logistic regression model assessed the impact of maternal age on preeclampsia without considering gestational diabetes (path c), while another model evaluated the relationship between maternal age and gestational diabetes (path a). The association between gestational diabetes and preeclampsia was also analyzed (path b). If gestational diabetes was found to completely mediate the relationship between maternal age and preeclampsia (path c'), it would indicate that the relationship was fully mediated, otherwise, it was partially mediated.

The prevalences of gestational diabetes and preeclampsia, adjusted by maternal age, were estimated using the “margins” command (Williams, 2012). A moderated mediation analysis was performed using the PROCESS macro version 4.2 for SPSS (Hayes, 2017), thus using the bootstrap method (5000 samples) to estimate the indirect effects and the moderated mediation index at a confidence interval of 95%. Significant results were regarded as those whose confidence interval excluded zero.

Results

The average age of participants in our sample was 27.15 ± 7.08 years, with the youngest age being 15 years and the oldest age being 47 years. The results of the Bonferroni multiple comparison indicated that patients aged 40 years and older had significantly higher blood glucose levels than their younger counterparts, including those aged younger than 35 years. Similarly, patients aged 35 to 39 years had significantly higher blood glucose levels than those aged less than 35 years. What is more, patients with preeclampsia experienced significantly higher blood sugar levels than patients without preeclampsia. Using the Student's t-test, we also discovered that patients with a family history of hypertension and hyperglycemia experienced significantly higher blood glucose levels, as shown in Table 1.

Table 1: Comparison of characteristic values for the sociodemographic and clinical data of patients based on the Student/ANOVA test

Parameter	Gestational diabetes
Age	
Age less than 35 years	0.5323±0.21 ^a
advanced maternal age	0.7816±0.27 ^b
very advanced maternal age	0.9636±0.20 ^c
Preeclampsia	
Yes	0.77±0.36 ^a
No	0.56±0.23 ^b
Family history of hypertension	
Yes	0.70±0.24 ^a
No	0.57±0.30 ^b
Family history of hyperglycemia	
Yes	0.67±0.27 ^a
No	0.57±0.24 ^b

Mean that do not share a letter are significantly different.

Binary Logistics Regression

The ORs (odds ratios) and 95% CIs for gestational diabetes and preeclampsia are presented in Figure 2. AMA [p-value < 0.01] and vAMA [p-value < 0.001] were associated with a significantly higher risk of preeclampsia in the unadjusted model (Figure 2a). Following adjustment (Figure 2b), vAMA [p-value < 0.01] and gestational diabetes [p-value < 0.001] were positively related to preeclampsia. In the other model (Figure 2c), parity [p-value < 0.01], AMA [p-value < 0.001], and vAMA [p-value < 0.01] were positively associated with gestational diabetes.

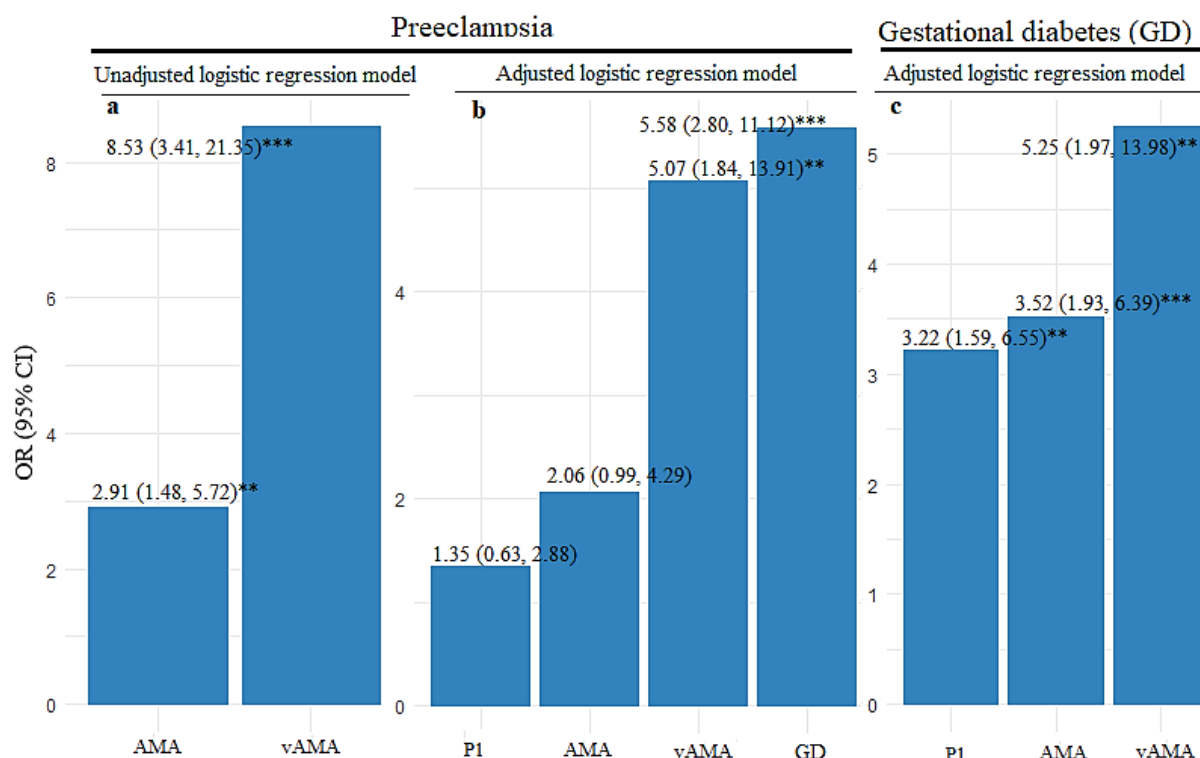


Figure 2: Univariate analysis of the association between maternal age and preeclampsia (a), as well as adjusted analysis between risk factors for preeclampsia and gestational diabetes (b & c). P1: multiparous; A: Age less than 35 years (reference category); AMA: advanced maternal age; vAMA: very advanced maternal age; GD: gestational diabetes. The last two models were adjusted for any family history of hypertension or hyperglycemia. ** $p < 0.01$, *** $p < 0.001$.

Prevalence of Gestational Diabetes and Preeclampsia

On analyzing the data from 700 full-term pregnancies, we observed that 12% of patients had gestational diabetes and 8% had preeclampsia. Once we investigated the prevalence of preeclampsia according to maternal age and gestational diabetes, some significant results emerged. After adjusting for any family history of hypertension and hyperglycemia, the prevalence of preeclampsia was significantly higher in patients with gestational diabetes [24.04%; $p < 0.001$], as well as in those of advanced or very advanced age [10.36%; $p < 0.001$; 20.38%; $p < 0.01$, respectively], as shown in Figures 3a and 3b.

On analyzing the prevalence of gestational diabetes according to maternal age and parity, some significant results were again observed. After adjusting for any family history of hypertension and hyperglycemia, the prevalence of gestational diabetes was significantly higher in women of advanced or very advanced age [21.85%; $p < 0.001$; 28.42%; $p < 0.01$, respectively], as well as in multiparous women [14.40%; 95% CI: 11.48, 17.33; $p < 0.001$]. The interaction between maternal age and parity revealed that among women of advanced and very advanced age, the risk of gestational diabetes increased almost sevenfold [26.89%; $p < 0.001$] when compared to patients younger than 35 years who were not multiparous [3.88%; $p < 0.01$]. In vAMA and multiparous patients, the risk increased almost ninefold (Figure 4a, 4b). Since the associations in the logistic models and predicted probabilities were found to be significant, a moderated mediation analysis could be considered later (Figure 1).

Testing for a Mediation Effect and Moderated Mediation Effect

Mediation analysis confirmed Hypothesis 1. As shown in Table 2, the regression coefficients reveal a relationship between maternal age and gestational diabetes [AMA: $\beta = 0.2485$; $p < 0.001$; vAMA:

$\beta = 0.4157$; $p < 0.001$], as well as another one between gestational diabetes and preeclampsia [$\beta = 2.1225$; $p < 0.05$], and these were significant after adjustment for any family history of hypertension and hyperglycemia. The bootstrapped indirect effect was 0.5275 [Boot CI %: 0.0151, 1.1258] in patients of an advanced age and 0.8824 [Boot CI %: 0.0266, 1.7895] in patients of a very advanced age. This confirms that an advanced or very advanced age is linked to gestational diabetes, which further increases the risk of preeclampsia, thus confirming Hypothesis 1.

To test Hypotheses 2 and 3, a moderated mediation analysis was performed. As expected, parity was found to moderate the relationship between maternal age and gestational diabetes (Table 3). The interaction between maternal age and parity had a significant effect on gestational diabetes (AMA x parity: $\beta = 0.2339$; $p < 0.001$ and vAMA x parity: $\beta = 0.2446$; $p < 0.05$). This indicates that the effect of an advanced or very advanced maternal age on gestational diabetes differed in patients according to the number of previous deliveries. Figure 5 shows the interaction patterns. The positive relationship between maternal age and gestational diabetes was stronger in patients with an advanced or very advanced age compared to those younger than 35, thus confirming Hypothesis 2.

Table 2: Results of mediation analysis (N =700).

Direct relationship	Dependent Variable : GD ($R^2=0.2365$, $p < 0.001$)		Dependent Variable : Preeclampsia ($R^2_{C\&S}= 0.062$; $R^2_{MCF}= 0.12$, $p < 0.001$)	
	β	95% CI	β	95% CI
Predictors				
Advanced maternal age vs. A	0.248 ^{***}	(0.202, 0.294)	0.5075	(-0.2674, 1.2824)
Very advanced maternal age vs. A	0.415 ^{***}	(0.328, 0.502)	1.1983	(0.1303, 2.2663)
Family history of hyperglycemia	0.054	(-0.000, 0.110)	0.2254	(-0.6160, 1.0669)
Family history of hypertension	0.083 ^{**}	(0.021, 0.146)	0.9708	(0.1278, 1.8138)
Gestational diabetes (GD)			2.1225 ^{**}	(0.8054, 3.4396)
Constant	0.083	(0.499, 0.536)	-4.3181	(-5.2247, -3.4114)
Relative conditional indirect effects of X on Y: Maternal age → Gestational diabetes → Preeclampsia				
Indirect relationship	Indirect effect	Boot SE	BootLLCI	BootULCI
Advanced maternal age vs. A	0.5275	0.2833	0.0151	1.1258
Very advanced maternal age vs. A	0.8824	0.4496	0.0266	1.7895

A: Age less than 35 years old; * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$.**

Table 3: Results of moderated mediation analysis (N =700).

Direct relationship	Dependent Variable: GD ($R^2=0.2770$, $p < 0.001$)		Dependent Variable: Preeclampsia ($R^2_{C\&S}= 0.0621$; $R^2_{MCF}= 0.1211$, $p < 0.001$)	
	β	95% CI	β	95% CI
Predictors				
Advanced maternal age vs. A	0.0863 [*]	(0.0061, 0.166)	0.507	(-0.2674, 1.282)
Very advanced maternal age vs. A	0.2194 [*]	(0.0320, 0.406)	1.198	(0.1303, 2.266)
Parity	0.0214	(-0.0153, 0.058)		
Advanced maternal age vs. A	0.2339 ^{***}	(0.1372, 0.330)		
Very advanced maternal age vs. A	0.2446 [*]	(0.0343, 0.454)		
Gestational diabetes (GD)			2.122	(0.8054, 3.439)
Family history of hyperglycemia	0.0557 [*]	(0.0018, 0.109)	0.225	(-0.6160, 1.066)
Family history of hypertension	0.0629 [*]	(0.0015, 0.124)	0.970	(0.1278, 1.813)

Constant		0.5055	(0.4750, 536)	-4.318	(-5.2247, -3.411)
Relative conditional indirect effects of X on Y: Maternal age → Gestational diabetes → Preeclampsia					
Indirect relationship		Indirect effect	Boot SE	BootLLCI	BootULCI
Maternal age	Parity				
AMA	Primiparity	0.1831	0.1560	-0.0338	0.5645
AMA	Multiparity	0.6795	0.3592	0.0201	1.4302
Index of Moderated Mediation		0.4964	0.2876	0.0103	1.1143
vAMA	Primiparity	0.4656	0.3251	-0.0725	1.1839
vAMA	Multiparity	0.9848	0.4977	0.0289	1.9925
Index of Moderated Mediation		0.5192	0.3677	0.0005	1.4035

A: Age less than 35 years old; AMA: Advanced maternal age; vAMA: Very advanced maternal age ; * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$.**

The results also confirmed the conditional indirect effect of parity. The moderated mediation index was 0.4964 [Boot CI %: 0.0103, 1.1143] for patients of an advanced age and 0.5192 [Boot CI: 0.0005, 1.4035] for patients of a very advanced age, indicating that the mediating effect of gestational diabetes on the relationship between maternal age and preeclampsia varies by parity. Among multiparous women, gestational diabetes mediated the relationship between advanced maternal age and preeclampsia [indirect effect = 0.6795, Boot CI %: 0.0201, 1.4302]. Furthermore, in women of very advanced age, the mediating effect of gestational diabetes was also significant (indirect effect = 0.9848, Boot CI %: 0.0289, 1.9925). Thus, Hypothesis 3 was confirmed. The final model is shown in Figure 5.

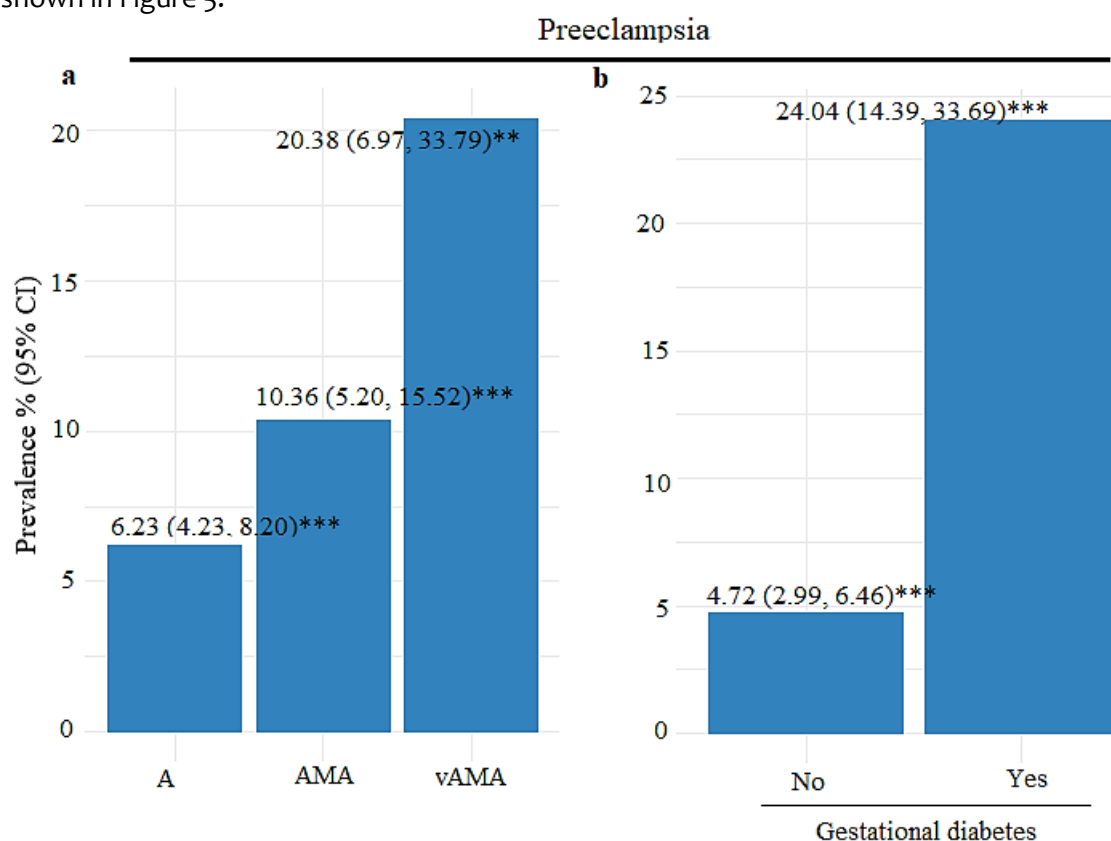


Figure 3: The adjusted prevalence (%) [95% CI] of preeclampsia in female patients.

A: Age less than 35 years old; AMA: advanced age; vAMA: very advanced age. The models were adjusted for any family history of hypertension and hyperglycemia.

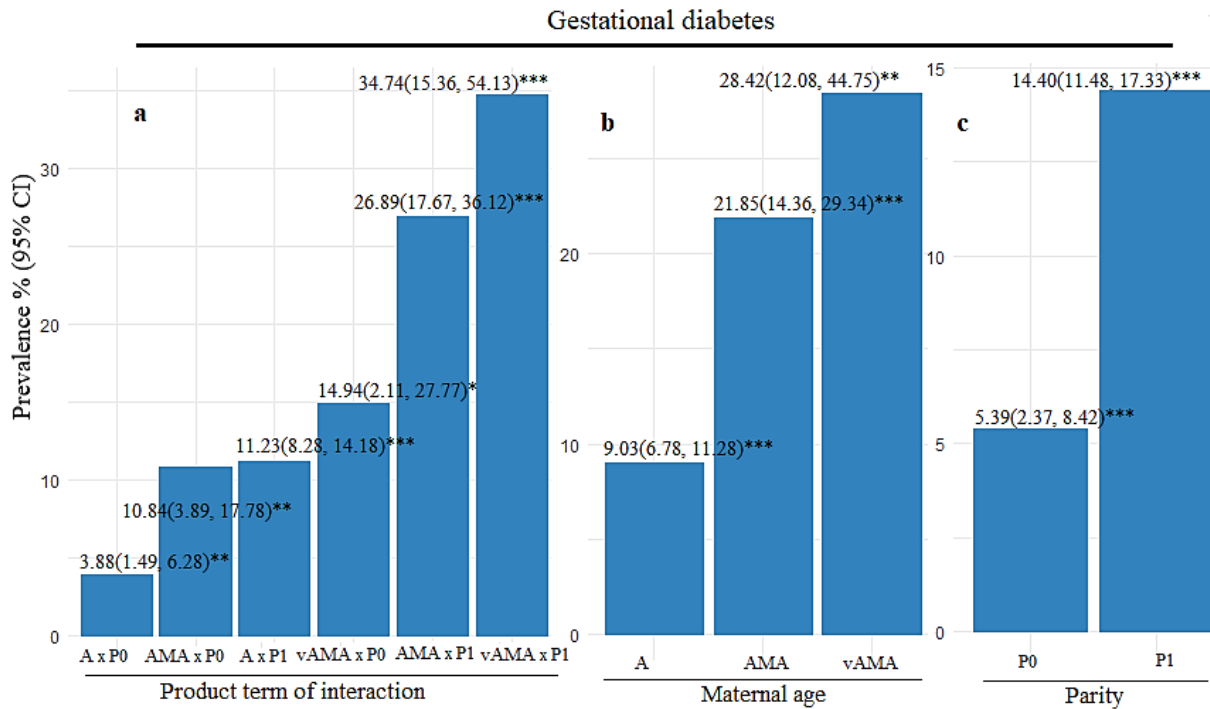


Figure 4: The adjusted prevalence (%) [95% CI] of gestational diabetes in patients.

A x P0: Age less than 35 years x primiparous; AMA x P0: advanced age x primiparous; A x P1: Age less than 35 years x multiparous; vAMA x P0: very advanced age x primiparous; AMA x P1: advanced age x multiparous; vAMA x p1: very advanced age x multiparous. The models were adjusted for any family history of hypertension and hyperglycemia.

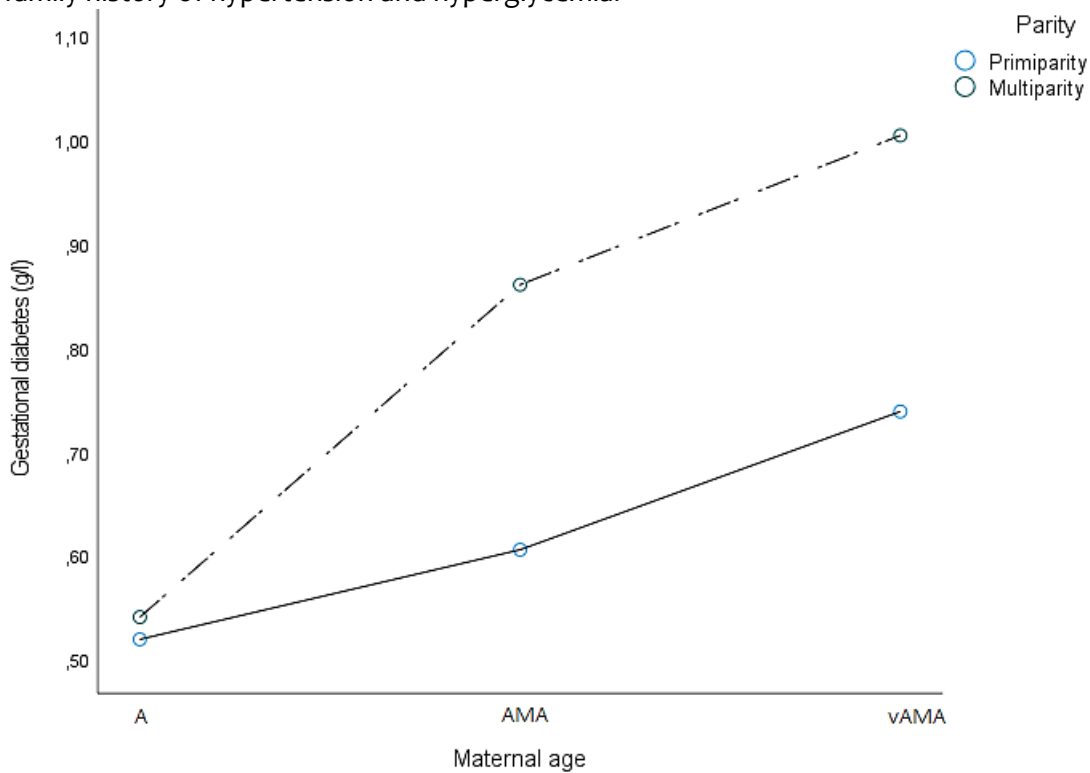


Figure 5: Influence of parity and gestational diabetes on preeclampsia.

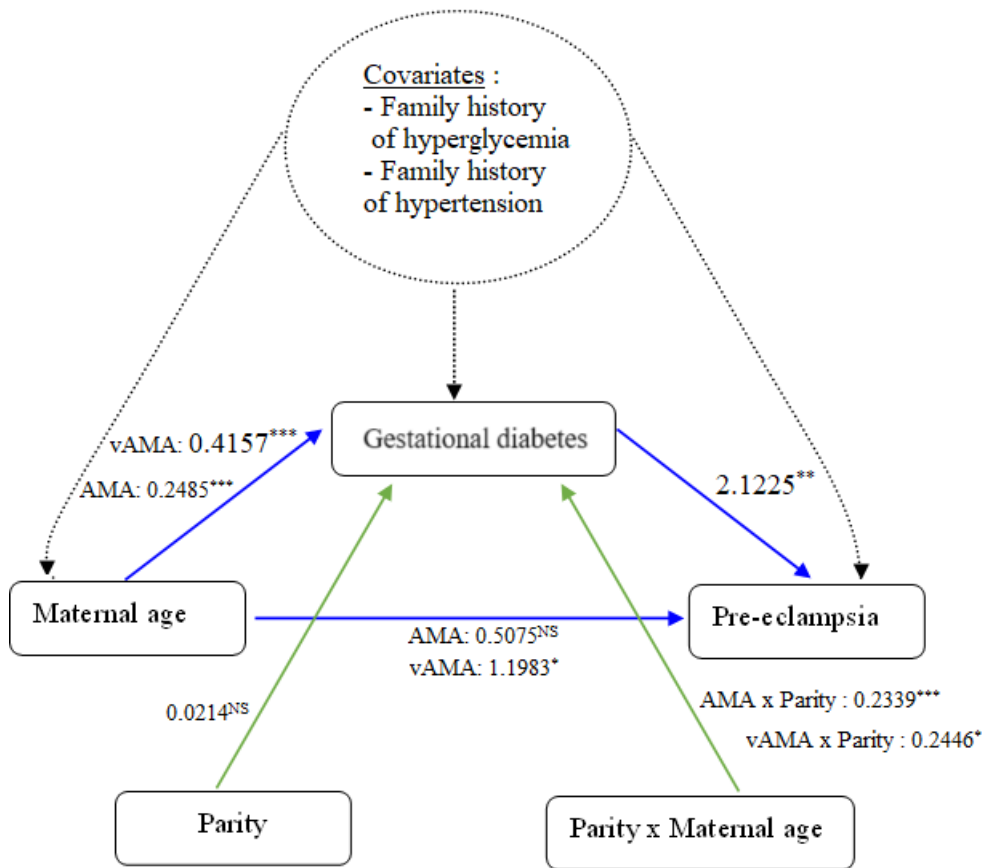


Figure 6: The final moderated mediation model.

Discussion

The Mediating Effect of Gestational Diabetes

Our study confirms a significant link between a very advanced maternal age and the risk of preeclampsia with there being a prevalence of 20.38% in women aged 40 and over, compared to 10.36% in women of an advanced age and 6.23% in women under 35 years old. These results are consistent with previous studies, although some research has reported conflicting findings. For example, Bartsch et al reported a 60% increase in the risk of preeclampsia in women over 40 years old (Bartsch et al., 2016), while Khalil et al and Claremont et al did not find any significant differences when compared to younger women (Claramonte Nieto et al., 2019; Khalil et al., 2013). The epidemiological inconsistencies in these results may be due to the use of relatively small samples in some of these studies, and multivariate analysis did not confirm these results ((Vincent-Rohfritsch et al., 2012).

There is also strong evidence for an increased risk of preeclampsia in women of advanced maternal age. For example, Poon et al observed an increased risk of preeclampsia from the age of 32, with this increasing by approximately 4% for each additional year (Poon et al., 2010). Khalil et al also noted a significant relationship between maternal age and the risk of preeclampsia, with there being an 8% higher risk among women aged 35 to 39 and a 50% higher risk among those aged 40 and older, even after adjusting for confounding variables (Khalil et al., 2013).

Meta-analyses that bring together data from millions of births have further confirmed these findings, with one showing a relative risk of 1.2 for women over 35 years old, 2.4 for those over 40 years old, and 3.6 for those over 45 years old (Lisonkova et al., 2017). Specific studies have reinforced these findings, such as that of Smithson et al, who observed a doubling of the risk in women over 45 compared to those aged 40 to 45 (Smithson et al., 2022). Recent surveys have also shown a doubling in the risk for women over 50 compared to those aged 40 to 49 (Schwartz et al., 2020).

In our study, women aged 35 to 39 were not significantly associated with a risk of preeclampsia, but this risk became 5.07 for women aged 40 and above.

However, other evidence shows that maternal ageing can lead to an inflammatory profile and elevated oxidative stress, which are linked to pregnancy complications, particularly placental dysfunction (Burton & Jauniaux, 2018). Older women without complications generally show a decline in anti-inflammatory cytokines, including IL-10 and IL-1RA, which are associated with increased antioxidant capacity. Low IL-10 levels in elderly mothers correlate with placental dysfunction, as had been confirmed for IL-10-deficient mice through an increased sensitivity to inflammatory stimuli (Chatterjee et al., 2011). It is therefore essential to further explore the relationship between ageing, reductions in anti-inflammatory cytokines, and the vulnerability of older women to adverse effects on placental function (Da Silva et al., 2012).

In older mothers with complications, the oxidative stress is elevated despite the increased antioxidant capacity (Lean et al., 2021). This suggests that significant oxidative damage is linked to inadequate antioxidant responses, leading to altered placental function after pregnancy complications (Myatt & Cui, 2004). Future studies are therefore needed to confirm the role that oxidative damage plays in placental dysfunction for older mothers.

Older women who developed complications show reduced levels of placental hormones (hPL, sFlt, PIGF), thus confirming placental dysfunction (Lean et al., 2021). There is evidence to suggest that these biomarkers are linked to placental dysfunction, particularly with preeclampsia (Kenny et al., 2014).

In brief, the studies' results support our conclusion that very advanced maternal age has a direct impact on the risk of pre-eclampsia, as shown in our final moderated mediation model illustrated in Figure 6.

Despite having a high antioxidant capacity, older mothers with complications experience strong oxidative stress, potentially damaging the placenta, and this is linked to inadequate antioxidant responses and placental alterations (Myatt & Cui, 2004), but future studies are needed to confirm these links.

PIGF represents a promising biomarker for predicting complications in older mothers (Heazell et al., 2019), but large-scale studies will be needed to develop an integrated prediction model, improve personalized care, and reduce complications without any unnecessary interventions.

The results of our study confirm that a very advanced maternal age is a significant predictor of preeclampsia, with gestational diabetes playing a mediating role. Indeed, maternal age directly influences preeclampsia, but it also has an indirect effect via gestational diabetes. Thus, this study highlights how gestational diabetes strengthens the link between an advanced or very advanced maternal age and preeclampsia.

Our results also provide further empirical evidence to support the notion that a very advanced maternal age plays a key role in predicting preeclampsia. Furthermore, it is important to highlight how gestational diabetes plays a mediating role in the link between maternal age and preeclampsia. Indeed, while maternal age has a direct impact on preeclampsia, it also has an indirect effect on gestational diabetes, indicating the mechanism by which gestational diabetes bridges the link between an advanced or very advanced maternal age and preeclampsia. More importantly, if an expectant mother's advanced maternal age is not addressed from the start, it may ultimately lead to her developing gestational diabetes, which if continued to be left unaddressed, could increase the risk of preeclampsia.

When assessing the prevalence and mediating effects of gestational diabetes, we found that 28.42% of vAMA women and 21.85% of AMA women developed gestational diabetes during their pregnancy, compared to just 9.03% of women aged less than 35 years. A previous study also found that the risk of gestational diabetes increased significantly with age, from 2% in women aged 20 to 21% in those aged 40 (Al Rowaily & Abolfotouh, 2010). This is consistent with our results and further confirms that the risk of gestational diabetes increases with maternal age. Furthermore,

our results suggest that gestational diabetes could potentially play a mediating role. The mediated proportion, which indicates the extent to which the total effect of the association with preeclampsia can be explained by gestational diabetes, was highest in pregnant women of advanced and very advanced maternal ages, reaching up to 50.96% and 42.41%, respectively.

Additionally, ages 35 and above were significantly associated with gestational diabetes. According to Schummers et al, there is a linear increase in the risk of gestational diabetes along with the age of the mother. Compared with women aged 20 to 24 years, the adjusted relative risks (RR) for women aged ≥ 35 years, ≥ 40 years, and ≥ 45 years are 3.2, 4.2, and 4.4 (Schummers et al., 2018), which reflects our conclusions. In contrast, a study in China reported a peak adjusted prevalence of gestational diabetes in women aged 30–34 years, followed by a decrease after age 35 (Zhang et al., 2011). This finding raises concerns by suggesting that gestational diabetes may be affecting more and more relatively young women.

Nevertheless, it should be noted that this study had a limited number of participants in the older group, so further research would be needed to confirm this trend. For their part, Carolan et al. examined the combined effect of increasing maternal age and ethnicity on rates of gestational diabetes, with their results revealing differences in gestational diabetes rates between women born in Asia and those born in other regions, namely Australia, Europe, Oceania, the United Kingdom, Africa, and the Middle East (Carolan et al., 2012).

Our results indicate that pregnant women of all ages should be screened for gestational diabetes, particularly in resource-limited settings. An optimal threshold for selective screening, however, could be set at 25 years.

Ageing is generally associated with systemic insulin resistance and gestational diabetes in women of childbearing age (Y. Li et al., 2020). With increasing age, lean muscle mass can decrease, while visceral fat increases. In turn, this decreased muscle mass can result in reduced glucose elimination in the body, leading to glucose intolerance (Barbieri et al., 2001).

In women with GDM, insufficient insulin secretion to counteract systemic insulin resistance is notable (Chiefari et al., 2017). What is more, ageing reduces the ability of pancreatic β cells to proliferate during pregnancy, potentially promoting GDM in pregnant women (Rieck & Kaestner, 2010). As mentioned above, the increase in systemic insulin resistance is mainly due to age-related changes related to skeletal muscle mass and visceral fat mass (Barbieri et al., 2001; Gautier et al., 1998). Nevertheless, the exact mechanisms causing this resistance remain to be identified, although hypoxia could be playing a role (Arcidiacono et al., 2021). Furthermore, a recent study confirmed that a high preconception BMI, which is indicative of visceral adiposity and insulin resistance, plays a key role in developing GDM, suggesting that it could be targeted through public health policies (Mirabelli et al., 2023).

Another Chinese study of a population of women with gestational diabetes aged 35 to 40 years opened up another avenue of research by suggesting that the underlying mechanism could potentially involve dysfunctions in amino acid and fatty acid metabolism, thus worsening insulin resistance. This study also found that the combination of several long-chain fatty acids and amino acids could be used to predict gestational diabetes in older women as early as the first trimester, but future research will of course need to confirm these metabolic markers. Furthermore, metabolic profiling provides valuable guidance for clinical obstetricians to provide specific advice about appropriate nutrition for women over 35 years of age with gestational diabetes (He et al., 2022).

Furthermore, women with gestational diabetes in our study appeared to be at a higher risk of developing preeclampsia. Even after controlling for confounding factors, gestational diabetes remained an important clinical determinant of preeclampsia. A previous study also showed that gestational diabetes increased the occurrence of preeclampsia, which is consistent with our study (J. Li et al., 2023). An international HAPO study of more than 23,000 pregnant women from nine countries revealed that hyperglycemia is positively linked to preeclampsia, even after adjusting for many factors (e.g., clinical centre, age, BMI, height, smoking, alcohol consumption, family history

of diabetes, etc.) (HAPO Study Cooperative Research Group, 2009). Nevertheless, some studies indicate that there is no independent link between gestational diabetes and preeclampsia after taking into account pre-pregnancy weight and other factors (Cheung et al., 2018; Košir Pogačnik et al., 2020).

In contrast, other studies have suggested that advanced age is not independently associated with the occurrence of preeclampsia in women with gestational diabetes (Osuagwu et al., 2020). Only one retrospective study has posited that an advanced age is an independent risk factor for preeclampsia in women with gestational diabetes (Yogev et al., 2004). Although gestational diabetes is associated with preeclampsia, the precise mechanism remains unclear. Indeed,

The underlying relationship between GDM and the occurrence of preeclampsia can be explained through various factors. Hyperglycemia triggers inflammation and the autophagy of trophoblasts, thus hindering their migration and invasion. GDM also leads to the hyperactivation of neutrophils that release excess neutrophil extracellular traps (NETs), thus reducing villous blood flow and causing preeclampsia-related placental ischemia. Furthermore, GDM increases oxidative stress, leading to a reduction in circulating nitric oxide (NO) and vasodilation dysfunction. Advanced glycation end-products (AGEs) also increase with GDM, thus promoting preeclampsia through oxidative stress and inflammation. Pro-inflammatory cytokines such as TNF- α and IL-6 are also elevated in women with GDM, and this contributes to endothelial dysfunction and preeclampsia (Yang & Wu, 2022).

Some research has indicated that TNF- α , IL-6, and C-reactive protein (CRP) are independent risk factors for preeclampsia in women with gestational diabetes (Barden et al., 2004; Žák & Souček, 2019). Others have suggested that in addition to elevated CRP levels, an imbalance between interleukin 17 and interleukin 35 may play a role in the development of preeclampsia in women with gestational diabetes (W. Cao et al., 2018).

Obesity is the main risk factor for preeclampsia in women with GDM, because this has been associated with oxidative stress, inflammation, and fatty acid imbalance (Lopez-Jaramillo et al., 2018). Furthermore, pre-pregnancy hyperinsulinemia and insulin resistance contribute to problems with cytotrophoblast migration and uterine spiral artery remodelling, thus increasing the risk of placental ischemia (Lopez-Jaramillo et al., 2018).

While some studies question the direct link between gestational diabetes and preeclampsia, particularly when taking pre-pregnancy weight into account, obesity has also been identified as a major risk factor for preeclampsia, because it exacerbates oxidative stress, inflammation, and disturbances in fat metabolism, with this being mainly due to pre-existing hyperinsulinemia and insulin resistance. Understanding this mechanism will be essential for identifying markers and developing preventive measures, so it warrants further research.

The Moderating Effect of Parity

As hypothesized, parity exhibited a positive moderating effect on the relationship between maternal age and gestational diabetes. In particular, when the maternal age was advanced (≥ 35 years) and very advanced (≥ 40 years), the risk of gestational diabetes was significantly higher in multiparous patients than in primiparous patients, highlighting how multiparity plays an important role in worsening the risk of gestational diabetes in older patients, as confirmed by other studies (Dai et al., 2023; Wagan et al., 2021).

Nevertheless, it should be noted that our findings differ from those of some previous work that has suggested that primiparity is a risk factor associated with gestational diabetes (Ben-David et al., 2016; Laine et al., 2018). It is important to note, however, that these contrasting results could be attributed to the fact that first-time women with a history of gestational diabetes have a 50% risk of recurrence in their subsequent pregnancies (Kruse et al., 2015). Although we did not take into account any history of gestational diabetes in this analysis, this parameter could potentially have explained the persistence of gestational diabetes in certain multiparous patients.

Furthermore, the effect of parity on the risk of gestational diabetes has also been associated with advanced age in patients, as a higher number of pregnancies tends to be observed in women of advanced maternal age (Dode & Santos, 2009). Additionally, several previous studies have revealed associations between advanced maternal age, pre-pregnancy adiposity, and the prevalence of gestational diabetes (Collier et al., 2017; Shin & Song, 2015). Furthermore, the results from a study that took into account the body mass index (BMI) showed that obese primiparous women had a five times higher risk of gestational diabetes than primiparous women with a normal BMI (Laine et al., 2018). Not taking into account the BMI in our study could partly explain the inconsistency in these results.

A possible explanation for the association between multiparity in older women and gestational diabetes could lie in how episodes of insulin resistance may contribute to the decline in β cell function because each pregnancy is characterized by an episode of insulin resistance (Yong et al., 2021). Similarly, Wang et al supplied additional evidence to show that multiparous women with gestational diabetes were more likely to have poor glycemic control (Wang et al., 2022). Given the negative impact of parity on the risk of gestational diabetes, multiparous women who develop gestational diabetes are advised to engage in greater physical activity to achieve optimal glycemic control (Wang et al., 2022). Indeed, the 2019 Canadian guidelines for physical activity during pregnancy recommend at least 150 minutes of moderate-intensity physical exercise per week for pregnant women. Nevertheless, we suggest that at least 60 minutes of moderate physical activity per week is sufficient for first-time mothers with gestational diabetes, while we recommend exercising at least 90 minutes per week for multiparous women (Obstetricians, 2015).

The Moderated Mediation Effect of Parity

Parity plays a central role in pregnancy complications, including gestational diabetes and preeclampsia. It also moderates the mediating effect of gestational diabetes in the relationship between maternal age and preeclampsia, although this effect is only significant in multiparous pregnant women. Increasing parity may lead to increased insulin requirements due to the intense demand on pancreatic β cells during pregnancy. These increased insulin requirements are influenced by various factors, such as maternal age, a high body mass index (BMI), and changes in placental hormonal secretion (Skajaa et al., 2018).

In summation, parity is a crucial element in determining how an advanced maternal age affects the risk of gestational diabetes, which in turn may aggravate the risk of preeclampsia. Understanding these complex interactions between maternal age, parity, gestational diabetes, and preeclampsia is essential for obstetric risk management. Health professionals must consider these relationships to ensure optimal maternal care and prevent complications during pregnancy.

Implications and Limitations

The results highlight the increased risks for women of advanced maternal age (AMA or vAMA) depending on their parity, with these having major implications for maternal healthcare and the prevention of obstetric complications. This study has limitations, however, such as its retrospective nature and the use of a sample from a single hospital. Diverse multicenter studies are therefore needed to establish more robust cause-and-effect relationships. Our results could also have been influenced by unmeasured factors that warrant further research.

In addition, the sample size is limited, which could affect the robustness of the results. Overall, it is essential to explore potential confounding factors—such as the pre-pregnancy BMI, multiple pregnancies, education level, and other variables—to gain a complete understanding of the links between maternal age, gestational diabetes, and preeclampsia. Finally, any generalization of the results to a larger population must be performed with caution given that the data originated from a single hospital.

Conclusion

In summary, this study confirms the significant impact of advanced maternal age on preeclampsia, particularly in women aged 40 and over. In addition, an advanced maternal age was linked to an increased risk of gestational diabetes, which appears to also mediate the relationship between an advanced maternal age and preeclampsia. Parity, meanwhile, acts as a moderator, with multiparous women at even greater risk of gestational diabetes and consequently preeclampsia. Overall, this study revealed a complex nexus between maternal age, parity, gestational diabetes, and preeclampsia, thus highlighting the need for tailored prevention and management strategies for optimal obstetric outcomes.

Nevertheless, it is important to emphasize that further research is imperative. For example, further exploration of the mechanisms that underlie these complex associations, particularly at the molecular and cellular level, is needed to improve our understanding of how maternal age, gestational diabetes, and preeclampsia interact.

It would also be beneficial to conduct randomized clinical trials aimed at evaluating the effectiveness of preventive interventions—such as through lifestyle modifications, dietary changes, and drug treatments—aimed at reducing the risk of developing gestational diabetes and, by extension, preeclampsia in older pregnant women.

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