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# Impact of fetal gender on the incidence of preeclampsia: A cohort study in Greece

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## Abstract

**Introduction:** Preeclampsia is associated with significant maternal and fetal morbidity and mortality, with established risk factors. Fetal gender has been proposed as a potential independent risk factor for preeclampsia, though its exact role is not yet determined as studies to date have reported conflicting results. This study aimed to investigate the association between fetal gender and preeclampsia while accounting for key confounders.

**Material and methods:** This retrospective cohort study was conducted at the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece, between December 2018 and March 2025. Data extracted from electronic medical records encompassed maternal demographics, obstetric history, pre-pregnancy weight and body mass index (BMI), use of assisted reproductive technologies (ART), smoking status, parity, aspirin usage and uterine artery Doppler findings (z-score and bilateral uterine artery notching). Preeclampsia was diagnosed according to standard clinical criteria, and fetal gender was determined during routine second-trimester ultrasound and confirmed at delivery. Multivariable logistic regression was used to assess the association between potential risk factors and preeclampsia, adjusting for potential confounders. Interaction analyses were performed to examine potential effect modification between fetal gender and maternal age>35 years, BMI>25 kg/m$^2$, smoking, and uterine artery Doppler indices.

**Results:** A total of 9,603 singleton pregnancies were included; 68 women (0.7%) developed preeclampsia. Following multivariable logistic regression, fetal gender was not associated with preeclampsia (aOR 1.02; 95% CI: 0.61–1.70; p=0.94). Significant predictors included ART (aOR 3.68; 95% CI: 1.72–7.50; p<0.001), higher pre-pregnancy BMI (aOR 1.07 per unit; 95% CI: 1.03–1.12; p<0.001), elevated uterine artery z-score (aOR 2.12; 95% CI: 1.71–2.63; p<0.001), and bilateral uterine artery notching (aOR 3.50; 95% CI: 1.54–7.50; p=0.002). Maternal age, smoking, parity, and aspirin use were not significantly associated with preeclampsia (all p>0.05). Interaction analyses revealed no statistically significant effect modification between male fetal

gender and maternal age>35 years (p=0.14), BMI>25 kg/m$^2$ (p=0.13), smoking (p=0.72), elevated uterine artery z-score (p=0.35), or bilateral uterine artery notching (p=0.30). Similarly, no significant interactions were observed between aspirin use and maternal risk factors or Doppler findings (all p>0.05). Analysis by BMI category also showed no statistically significant interactions in any subgroup (all p>0.05).

**Conclusion:** Fetal gender was not associated with increased risk of preeclampsia and did not modify maternal or uteroplacental factors. Pre-pregnancy maternal BMI, use of ART and abnormal uterine artery Doppler findings were confirmed as key predictors of preeclampsia. Clinical risk assessment should continue to focus on maternal and placental characteristics rather than fetal gender.

**Key words:** Fetal gender, preeclampsia, body mass index, assisted reproductive technologies, smoking, maternal age, aspirin, uterine artery Doppler

## Introduction

Preeclampsia is a hypertensive disorder of pregnancy, characterized by new onset hypertension (BP>140/90mmHg), commonly after 20 weeks of gestation and end organ damage, is considered a major complication of pregnancy, affecting approximately 5-8% of pregnancies worldwide and remains a leading cause of both fetal and maternal morbidity and mortality[1,2].

The exact pathophysiology of preeclampsia remains poorly understood, though risk factors including maternal age, pre-existing hypertension, kidney disease, nulliparity, obesity and gestational diabetes mellitus are well established[3-6]. Multiple studies have shown that an increased BMI before pregnancy increases the risk of preeclampsia through various possible mechanisms such as chronic inflammation, oxidative stress, endothelial dysfunction, and insulin resistance[7,8].

In early pregnancy, maternal characteristics (such as chronic kidney disease, autoimmune diseases, diabetes mellitus, chronic hypertension, maternal age and race, BMI, previous history or family history of preeclampsia) and biomarkers (such as mean arterial pressure and serum placental growth factor) are used to estimate preeclampsia risk and stratify women accordingly[9-11]. A low-dose of aspirin (150mg) is recommended in women identified as high-risk for preeclampsia(risk cut off 1/150 in a predominantly white population)[12]. Provided treatment is initiated before 16 weeks of gestation, a significant reduction in the incidence and severity of preeclampsia is described[13]. A useful screening tool for the prediction of preeclampsia, in addition to maternal and fetal characteristics, some of which are described above, is offered by the application of Doppler ultrasound of the uterine arteries. Elevated pulsatility index (PI) and subsequently elevated z-score and the persistence of bilateral notching beyond the first trimester reflect impaired trophoblastic invasion and abnormal spiral artery remodeling, as well as increased resistance in the uteroplacental circulation, all of which are proposed as key mechanisms implicated in the pathogenesis of preeclampsia[14-16].

Given that fetal gender influences several adverse obstetric outcomes, it is reasonable to question whether similar sex-specific patterns exist for preeclampsia. Male fetal gender has been found to be associated with negative obstetric outcomes, such as an increased risk for caesarean section, preterm birth and premature rupture of membranes, gestational diabetes mellitus, stillbirth and lower Apgar scores[17-19]. These differences might be due to immune response, placentation or metabolic variability between male and female fetuses[20,21].

This study aimed to explore the association between fetal gender and the risk for preeclampsia, accounting at the same time for potential confounding factors, as the ones described above.

## Materials and methods

### *Study design and population characteristics*

The present retrospective cohort study was conducted at the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece between December 2018 and March 2025. Eligible participants had complete clinical and demographic data relevant to the study objectives. Ethical approval was not required, as the study involved anonymized, routinely collected clinical data and did not interfere with patient management. The data were handled in compliance with institutional data protection policies and relevant regulations. Exclusion criteria included multiple pregnancies, pre-existing hypertension or diabetes mellitus, severe maternal comorbidities (cardiac or renal failure, autoimmune disorders), maternal age<18 years, and incomplete or missing medical records.

### *Diagnosis of preeclampsia*

Preeclampsia was diagnosed based on standard clinical criteria in accordance with the guidelines of the American College of Obstetricians and Gynecologists (ACOG)[22]. It was defined as new-onset hypertension (systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg on two occasions at least 4 hours apart) after 20 weeks of gestation, accompanied by proteinuria (≥300 mg in a 24-hour urine collection or a protein/creatinine ratio ≥0.3), or in the absence of proteinuria, the presence of signs of end-organ dysfunction, including thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances. Diagnosis was confirmed by the attending physician and recorded in the electronic medical records.

### *Data collection*

Data were obtained from electronic medical records and included detailed information on maternal demographic characteristics, anthropometric measurements, obstetric history, and fetal outcomes. Key variables of interest were maternal age, height, weight, BMI before pregnancy, parity, smoking status, use of ART, aspirin use, uterine artery z-score, and bilateral artery notching. Pre-pregnancy BMI was calculated using self-reported pre-pregnancy weight and measured height. Fetal gender was determined via second-trimester routine ultrasound and confirmed at delivery.

### *Statistical Analysis*

Descriptive statistics were used to summarize population characteristics. For continuous variables, normality was assessed using the Shapiro–Wilk test (for sample sizes<50) or the Kolmogorov–Smirnov test (for sample sizes ≥50). Variables following a normal distribution are reported as means with standard deviations (SD), while non-normally distributed variables are presented as medians with interquartile ranges (IQR). Comparisons between groups were conducted using independent-sample *t*-tests for normally distributed variables and the Mann–Whitney *U* test for non-normal distributions. Categorical variables were compared using the chi-squared test or Fisher's exact test when expected cell counts were below 5. To evaluate the association between fetal gender (male vs. female) and the risk of preeclampsia, adjusted logistic regression analyses were performed. Adjusted models controlled for maternal age, pre-pregnancy BMI, parity, smoking status, and the use of ART. Effect estimates are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI).
To assess whether the effect of fetal gender on pre-

eclampsia risk varied by specific maternal characteristics, interaction terms were introduced into the models for the following factors: maternal age (>35 years), pre-pregnancy BMI, smoking status, uterine artery z-score, and bilateral artery notching. Additive interactions were further evaluated using the Relative Excess Risk due to Interaction (RERI). BMI categories were defined according to WHO standards: underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$) and obese (≥30 kg/m$^2$).[23] Statistical significance was set at $p$<0.05. All analyses were conducted using R statistical software.

## Results

The study population consisted of 9,603 pregnant women, categorized into a preeclampsia group (n=68) and a non- preeclampsia group (n=9,535) based on clinical diagnosis. Table 1 presents the characteristics of the study population stratified by the presence or absence of preeclampsia. Women who developed preeclampsia (n=68) had a higher median pre-pregnancy weight compared with the non- preeclampsia group (69 kg [62–82] vs. 63 kg [57–73], p=0.001). Pre-pregnancy BMI was also significantly higher in the preeclampsia group (26.2 [22.6–30.6] vs. 23.0 [20.8–26.4], p<0.0001). BMI category analysis showed that women with preeclampsia were more likely to be obese (28.1% vs. 13.3%, p=0.001) or overweight (31.3% vs. 19.7%, p=0.03) pre-pregnancy, while the proportion of those with normal pre-pregnancy BMI was lower (34.4% vs. 62.3%, p<0.0001). Maternal age did not differ significantly between groups (32.5 ±6.5 vs. 31.6 ±5.3 years, p=0.26), nor did the proportion of women older than 35 years (35.3% vs. 26.3%, p=0.12). Parity also did not reach statistical significance (29.4% vs. 41.8%, p=0.052). In contrast, use

Table 1. Baseline characteristics of the study population.

| MATERNAL VARIABLE | NON-PREECLAMPSIA (N=9,535) | PREECLAMPSIA (N=68) | P-VALUE |
|---|---|---|---|
| Maternal age (years) | 31.64 (±5.27) | 32.53 (±6.45) | 0.26 |
| Maternal age>35 (%) | 2503 (26.25%) | 24 (35.29%) | 0.12 |
| Weight pre-pregnancy | 63 (57,73) | 69 (62,82) | 0.001 |
| Pre-pregnancy BMI (median IQR) | 23 (20.8,26.4) | 26.2 (22.58,30.57) | <0.0001 |
| Pre-pregnancy BMI underweight (%) | 402 (4.72%) | 4 (6.25%) | 0.78 |
| Pre-pregnancy BMI normal weight (%) | 5,305 (62.29%) | 22 (34.37%) | <0.0001 |
| Pre-pregnancy BMI obese (%) | 1,136 (13.34%) | 18 (28.13%) | 0.001 |
| Pre-pregnancy BMI overweight (%) | 1,673 (19.65%) | 20 (31.25%) | 0.03 |
| Parity (%) | 3,986 (41.8%) | 20 (29.41%) | 0.052 |
| ART use (%) | 501 (5.25%) | 14 (20.59%) | <0.0001 |
| Smoking (%) | 1,032 (10.82%) | 7 (10.29%) | 0.1 |
| Male fetal gender (%) | 4,896 (51.89%) | 35 (52.24%) | 0.1 |
| Female fetal gender (%) | 4,539 (48.11%) | 32 (47.76%) | 0.1 |

*BMI: Body Mass Index; ART: Assisted Reproductive Technology; Continuous variables are presented as mean ± standard deviation (for normally distributed data) or median (interquartile range) as appropriate; categorical variables are expressed as frequencies and percentages. Comparisons between groups were performed using the independent samples t-test or Mann–Whitney U test for continuous variables, and the chi-squared or Fisher's exact test for categorical variables. A p-value<0.05 was considered statistically significant. "–" denotes not enough data to perform statistical comparisons.

of ART was significantly higher in the preeclampsia group (20.6% vs. 5.3%, p<0.0001). Smoking status on the other hand, (10.3% vs. 10.8%, p=0.1) and fetal gender distribution (male: 52.2% vs. 51.9%, p=0.10; female: 47.8% vs. 48.1%, p=0.10) were not significantly different between groups. Asshownin Table 2, fetal gender was not significantly associated with preeclampsia (aOR 1.02, 95% CI 0.61–1.70, p=0.94). In contrast, conception via ART was independently associated with a significantly higher risk of preeclampsia (aOR 3.68, 95% CI 1.72–7.50, p<0.001), as was higher pre-pregnancy BMI (aOR 1.07, 95% CI 1.03–1.12, p<0.001). Regarding uterine artery Doppler findings, a higher uterine artery z-score (aOR 2.12, 95% CI 1.71–2.63, p<0.001) and the presence of bilateral uterine artery notching (aOR 3.50, 95% CI 1.54–7.50, p=0.002) were both associated with increased risks. Other maternal and pregnancy-related factors were not significantly associated with preeclampsia, including maternal age (aOR 1.01, 95% CI 0.96–1.06, p=0.65), smoking (aOR 0.94, 95% CI 0.38–2.00, p=0.89), parity (aOR 0.62, 95% CI 0.34–1.10, p=0.11), and low-dose aspirin use (aOR 1.37, 95% CI 0.73–2.48, p=0.31).

Table 3 shows the interaction analyses for male fetal gender with maternal risk factors and Doppler measurements. No statistically significant interactions were observed between male fetal gender and

Table 2. Factors associated with preeclampsia.

| FACTORS | AOR (95% CI) | P-VALUE |
|---|---|---|
| Maternal age (years) | 1.01 (0.96–1.06) | 0.65 |
| Pre-pregnancy BMI (kg/m$^2$) | 1.07 (1.03–1.12) | <0.001 |
| Male fetal gender | 1.02 (0.61–1.70) | 0.94 |
| ART use | 3.68 (1.72–7.50) | <0.001 |
| Aspirin use | 1.37 (0.73–2.48) | 0.31 |
| Uterine artery z-score | 2.12 (1.71–2.63) | <0.001 |
| Bilateral uterine artery notching | 3.50 (1.54–7.50) | 0.002 |
| Smoking | 0.94 (0.38–2.00) | 0.89 |
| Parity | 0.62 (0.34–1.10) | 0.11 |

*Adjusted odds ratios (aOR) and 95% confidence intervals (CI) are derived from multivariable logistic regression analysis. The model included maternal age, pre-pregnancy Body Mass Index (BMI), fetal gender, Assisted Reproductive Technology (ART) use, smoking, parity, aspirin use, uterine artery z-score, and bilateral artery notching. A p-value<0.05 was considered statistically significant.

Table 3. Interaction between fetal gender and maternal risk factors on preeclampsia risk.

| EXPOSURE COMBINATION | JOINT EFFECT (AOR) | RERI | P-VALUE FOR INTERACTION |
|---|---|---|---|
| Male fetus × Maternal age>35 | 1.41 | 0.80 | 0.14 |
| Male fetus × BMI>25 | 2.34 | 1.02 | 0.13 |
| Male fetus × Smoking | 1.09 | 0.28 | 0.72 |
| Male fetus × Uterine artery z-score | 2.92 | -0.07 | 0.35 |
| Male fetus × bilateral uterine artery notching | 19.31 | 8.99 | 0.30 |

*Joint Effect (aOR) refers to the odds ratio for the combined exposure (male fetus and specified BMI category). RERI: Relative Excess Risk due to Interaction. P-values represent significance of interaction on the multiplicative scale. Smoking was assessed as a binary variable. BMI: Body Mass Index.

Table 4. Interaction between fetal gender and maternal BMI categories on pre-eclampsia risk.

| EXPOSURE COMBINATION | JOINT EFFECT (AOR) | RERI | P-VALUE FOR INTERACTION |
|---|---|---|---|
| Male fetus × Underweight | 1.43 | –3.84 | 0.25 |
| Male fetus × Normal BMI | 0.33 | –0.34 | 0.31 |
| Male fetus × Overweight | 1.85 | 1.15 | 0.10 |
| Male fetus × Obese | 1.09 | –0.03 | 0.95 |

*Joint Effect (aOR) refers to the odds ratio for the combined exposure (male fetus and specified BMI category). RERI: Relative Excess Risk due to Interaction. P-values represent significance of interaction on the multiplicative scale.

maternal age>35 years (aOR 1.41; p=0.14), pre-pregnancy BMI>25 kg/m$^2$ (aOR 2.34; p=0.13), or smoking (aOR 1.09; p=0.72). Similarly, no significant interactions were found between male fetal gender and uterine artery Doppler indices, including elevated uterine artery z-score (aOR 2.92; p=0.35) or bilateral artery notching (aOR 19.31; p=0.30).

Interaction analyses between fetal gender and pre-pregnancy BMI categories in relation to pre-eclampsia risk are presented in Table 4. No statistically significant interactions were observed in any BMI category. Among underweight women, the joint effect estimate was aOR 1.43 (RERI –3.84; p=0.25). For women with normal BMI, the joint effect was aOR 0.33 (RERI –0.34; p=0.31). In the overweight group, the joint effect was aOR 1.85 (RERI 1.15; p=0.10). Among obese women, the joint effect was aOR 1.09 (RERI –0.03; p=0.95).

## Discussion

### *Main findings*

The present study showed that: 1) Fetal gender was not an independent risk factor for the development of preeclampsia, 2) use of ART, higher pre-pregnancy maternal BMI, and abnormal Doppler findings (elevated uterine artery z-score and bilateral artery notching) each independently increased the risk for preeclampsia, 3) smoking status, parity and maternal age were not significantly associated with preeclampsia, 4) no statistically significant interactions were observed between fetal gender, maternal age greater than 35 years old, smoking, maternal BMI or uterine artery Doppler indices.

### *Interpretation of findings*

This study contributes to the existing literature as it illustrates the complex relationship between fetal gender and preeclampsia and the effect that certain maternal and pregnancy-related factors such as BMI, use of ART and uterine artery Doppler have in the presentation and prediction of the pathology. The principal finding, that fetal gender alone is not significantly associated with the risk of preeclampsia agrees with Mirzakhani and Weiss' study that found no association between the two[24]. Interestingly, the authors found an elevated risk for preeclampsia only in African American women carrying a male fetus, demonstrating that maternal race could possibly contribute, when combined with fetal gender, to the expression of preeclampsia. A 2016 systematic review and meta-analysis by Jaskolka et al. adds to this, as it was found that pregnant women, only in the non-Asian population, carrying a male fetus had a higher preeclampsia risk. However, when all 22 studies of the meta-analysis were included in the results there was no significant association between fetal gender and maternal risk of preeclampsia. These deviations could also be attributed to the variability in the definition of preeclampsia among the studies, as well as diverse study methods and demographics such as maternal race. There was also high heterogeneity between the studies and a lot of them did

not account for additional confounding factors, such as BMI and age, which could potentially explain the different outcomes[25].

Another hypothesis focuses on the different effect fetal gender might have on preeclampsia risk based on gestation age. A meta-analysis in 2020 studied the effect of fetal gender on maternal pregnancy outcomes (preeclampsia, eclampsia, gestational diabetes and other pathologies), with interesting results as far as preeclampsia is concerned. It was found that preterm preeclampsia was associated with female fetal gender, while pregnancies with male fetuses were associated with term preeclampsia[26]. These findings support the existence of a time diverse pattern of sexual dimorphic differences in preeclampsia. Adding to this, vascular adaptation also appears to vary by fetal gender, with higher uterine artery PI in women carrying a male fetus and gestational age–dependent blood pressure changes. Elevated diastolic blood pressure in the beginning of the pregnancy was observed among women carrying female fetuses with a shift after 24 weeks of gestation in favor of male fetuses[27]. This time-diverse pattern is supported by another recent study, with higher prevalence for preterm preeclampsia in pregnancies with a female fetus, but no difference in term or overall preeclampsia risk between the genders[28]. Our results are in line with the last half of the study, unfortunately data about the exact gestational age when preeclampsia occurred are not available in our cohort, so a comparison of results on that front was not able to be conducted.

In our study, both bilateral uterine artery notching and elevated uterine artery z score were independently associated with an increased risk of preeclampsia. These findings are consistent with previous evidence showing that impaired uteroplacental perfusion, reflected by abnormal Doppler indices, is linked with the pathogenesis of preeclampsia; bilateral notching has been linked to impaired remodeling of the spiral arteries, while an elevated PI reflects persistent high impedance to flow, both of which predispose to placental hypoxia and endothelial dysfunction[29]. Papageorghiou et al. demonstrated that both an elevated uterine artery PI and the presence of bilateral notches in the uterine artery waveform during the second trimester was significantly associated with the subsequent development of preeclampsia and fetal growth restriction[30]. Similarly, a large systematic review and meta-analysis by Cnossen et al. confirmed that increased uterine artery PI and the presence of notching were predictive of preeclampsia, particularly when assessed in the second trimester[14].

Our finding of an increased risk for preeclampsia in pregnancies conceived via ART is consistent with prior reports in the literature. Several large cohort studies and meta-analyses have demonstrated that the use of ART is associated with higher rates of hypertensive disorders of pregnancy, including preeclampsia, compared with spontaneously conceived pregnancies[31,32]. A systematic review and meta-analysis in 2019, incorporating 48 cohort and case-control studies reported that the risk for preeclampsia was 1.71 times higher among ART pregnancies compared with women who conceived spontaneously[33]. Proposed mechanisms included altered placentation and transfer practices, epigenetic modifications during early embryogenesis, and underlying subfertility or advanced maternal age, which are themselves risk factors for preeclampsia.

Maternal smoking was not associated with preeclampsia, in our cohort, differing from earlier meta-analyses indicating a protective effect[34,35]. Several explanations have been proposed for these divergent findings, with one important consideration being selection bias. Smoking is associated with an increased risk of early pregnancy loss[36], which may preferentially remove women at high risk of

preeclampsia from the denominator, artificially lowering preeclampsia incidence among ongoing pregnancies. Another potential explanation relates to exposure intensity. A dose dependent reduction in preeclampsia risk has been reported, with heavier smoking linked to a stronger effect[37]. However, accurate assessment of smoking exposure is challenging, as some women reduce their cigarette consumption during pregnancy or underreport their use. Such misclassification could contribute to inconsistencies across studies. Finally, confounding socioeconomic or metabolic factors that correlate with smoking status might influence results differently across populations.

The low incidence of preeclampsia in our cohort likely limited the statistical power to detect modest protective effects of aspirin, which are known to be greatest in high-risk populations and when initiated early in pregnancy. The ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial, demonstrated that low-dose aspirin (150 mg daily) initiated between 11 and 14 weeks of gestation significantly reduced the incidence of preterm preeclampsia by approximately 60% in high-risk women identified through first-trimester screening[12]. Furthermore, a secondary analysis of the ASPRE trial indicated that the beneficial effect of aspirin was highly dependent on patient compliance, with a 76% reduction in preterm preeclampsia observed in women with over 90% adherence compared to those with lower compliance[38]. These findings underscore the importance of early initiation and consistent adherence to aspirin therapy in effectively preventing preeclampsia. As such, variation in timing of initiation and patient adherence may have further attenuated any potential effect, contributing to the absence of a significant association in our study.

This study has certain limitations; its retrospective nature should be considered as the major one. Moreover, the single-center design, as well as the relatively small incidence of preeclampsia, which is however in accordance with the literature, may not allow the generalizability of the findings.

## Conclusions

This study adds to the growing body of literature on preeclampsia by clarifying the relative contributions of maternal, fetal, and pregnancy-related factors. Fetal gender was not independently associated with preeclampsia risk. In contrast, higher pre-pregnancy BMI, conception through ART and abnormal uterine artery Doppler findings (bilateral notching and elevated z-score were each independently associated with increased preeclampsia risk. Collectively, our results stress the importance of maternal risk stratification at the beginning of the pregnancy with the existing screening models, while highlighting the need for larger, multicentral cohorts to further explore subgroups and possible biological interactions and to offer a more precise assessment of risk.

## Conflict of interest

None.

## Funding

No.

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