

## Distinctive patterns of placental lesions in preeclampsia versus fetal growth restriction and their association with fetoplacental Doppler

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**Contribution****What does this work add to what is already known?**

Our study provides a comprehensive description of the placental lesions according to a systematic classification in the different clinical PE and/or FGR phenotypes, establishing also the association with fetoplacental Doppler.

**What are the clinical implications of this work?**

The placenta is an essential organ for the understanding of most relevant obstetric complications, revealing different placental lesions associated with the corresponding clinical presentation and fetoplacental Doppler.

## ABSTRACT

**Objectives:** The aim of this study was to describe placental histopathological findings in a large cohort of pregnancies complicated by preeclampsia and/or fetal growth restriction, and to investigate its association with fetoplacental Doppler.

**Methods:** This was a prospective observational study including pregnancies complicated by: 1) normotensive FGR defined as birthweight <10<sup>th</sup> centile (n=184); 2) PE with normally growth fetuses (n=102); 3) PE&FGR (n=120); and 4) uncomplicated pregnancies (n=202). Uterine, umbilical and middle cerebral artery pulsatility indices (PI) were assessed. Cerebroplacental ratio (CPR) was calculated by dividing the middle cerebral artery PI by the umbilical artery PI. Abnormal parameters were considered when PI >95<sup>th</sup> centile for uterine and umbilical artery, or <5<sup>th</sup> centile for middle cerebral artery and CPR. Placental lesions were categorized to vascular (maternal/fetal side), inflammatory and other lesions according to the 2014 Amsterdam Placental Workshop Group Consensus Statement. Univariate and multiple regression analysis were performed for the comparison between the study groups. Logistic regression was used to determine abnormal Doppler association with placental lesions.

**Results:** Maternal side vascular lesions are significantly higher in PE compared to controls and normotensive FGR (PE&FGR: 73%, PE: 46%, FGR: 38% vs. controls: 31%; p=0.01) including 2 types of lesions: developmental (PE&FGR: 13%, PE: 5%, FGR: 3% vs. controls: 2%, p<0.001) and malperfusion (PE&FGR: 70%, PE: 39%, FGR: 32% vs. controls: 25%, p=0.001). In contrast, fetal side developmental lesions are significantly higher in normotensive FGR compared to controls and PE (PE&FGR: 0%, PE: 3%, FGR: 8% vs. controls 2%, p=0.001). All cases displayed lower prevalence of infectious lesions, with a high prevalence of immune lesions in PE&FGR (PE&FGR:

17.5%, PE: 7.8%, FGR: 9.8% vs. controls 9.4%,  $p=0.001$ ). All fetoplacental Doppler parameters are associated with maternal side vascular lesions -mainly malperfusion- [uterine arteries mean PI (Odds ratio(OR)=2.45, 95% confidence interval (CI): 1.51 – 3.97), umbilical artery PI (OR=2.05, 95% CI: 1.02 – 4.47), middle cerebral artery PI (OR=2.75, 95% CI: 1.4 – 5.42), CPR (OR=1.75, 95% CI: 1.04 – 2.95)]. This association was evident mainly in the FGR groups -with and without PE-, being nonsignificant in controls or PE without FGR. No significant associations were observed between fetoplacental Doppler parameters and other placental lesions in any of the study groups.

**Conclusions:** PE and FGR exhibit different patterns of placental histopathological lesions in accordance with the clinical manifestation of the placental disorder (maternal vs. fetal). Fetoplacental Doppler shows an association with placental malperfusion lesions in the maternal side, reinforcing its use as a surrogate of placental insufficiency.

## Introduction

Preeclampsia (PE) and fetal growth restriction (FGR) are considered "great obstetrical syndromes" being responsible for short and long-term detrimental health consequences for both the mother and the fetus.<sup>1</sup> PE is a multisystem disorder that affects 2-5% of pregnancies<sup>2</sup> and is a leading cause of maternal and perinatal morbidity and mortality.<sup>3,4</sup> FGR, defined as the failure to achieve the endorsed fetal growth potential, affects 7-10% of all pregnancies<sup>5</sup> and is associated with poor perinatal outcomes<sup>6,7</sup> and long-term health consequences.<sup>8,9</sup>

Placental insufficiency is the most commonly accepted mechanism in both PE and FGR.<sup>10</sup> However, the diverse clinical phenotypes of these two conditions may exhibit different patterns of placental lesions.<sup>11,12</sup> Clinical and experimental evidence suggest that abnormal trophoblast invasion with a failure of physiological transformation of the spiral arteries is responsible for placental maldevelopment and impaired perfusion, which subsequently leads to placental insufficiency.<sup>13-15</sup> However, the differential pathways that lead to a systemic maternal disease (PE) or to a restrained condition compromising the transfer of nutrients and oxygen to the fetus (FGR), have not been elucidated. Pathological evaluation of the placenta could be particularly relevant to reveal the differences of these two conditions; however, it's limited by the heterogeneity in the taxonomy of placental lesions. In 2014, the Amsterdam Placental Workshop Group Consensus Statement recommended a standardized approach to describe histopathological placental findings,<sup>16</sup> which was endorsed by several authors<sup>17</sup> and intended to reduce the variability in placental examinations. Although many studies have reported the placental histopathology in PE<sup>15,18,27,28,19-26</sup> or FGR<sup>29-36</sup>, none of them relied on a systematic agreed-upon classification.

Fetoplacental Doppler is used widely in the clinical monitoring of PE and FGR, but still there is a gap of knowledge regarding what type of placental lesions is associated with abnormal Doppler. The aim of this study was to characterize placental histopathological lesions using this new classification in a large prospective cohort of pregnancies complicated by PE and/or FGR. As a secondary objective, we planned to investigate the association of fetoplacental Doppler with placental lesions.

## Methods

### *Study population*

This was a prospective observational study including all singleton gestations with a diagnosis of PE and/or FGR that attended at the Departments of Maternal-Fetal Medicine at BCNatal (Barcelona, Spain) between January 2014 and June 2017. FGR was defined as a birthweight below the 10<sup>th</sup> centile according to local standards including small for gestational age fetuses (when the birthweight was between the 3<sup>rd</sup> and the 9<sup>th</sup> centile) and those considered as growth restricted (with a birthweight <3<sup>rd</sup> centile and/or abnormal mean uterine arteries (UtA) pulsatility index (PI) and/or abnormal cerebroplacental ratio (CPR)).<sup>37</sup> PE was defined as high blood pressure (systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg on two occasions, at least four hours apart), developed after 20 weeks of gestation, with proteinuria ( $\geq 300$  mg/24 hours).<sup>2,38</sup> Controls were randomly selected from uncomplicated low-risk pregnancies with normotensive mothers and an appropriate for gestational age fetus (confirmed birthweight above 10<sup>th</sup> centile). Spontaneous preterm deliveries without clinical signs of infection, or iatrogenic preterm deliveries due to placenta previa were recruited as preterm controls. Preterm deliveries were considered when gestational age at delivery was  $\geq 24$  and <37 weeks gestation including both early and late preterm deliveries. Term deliveries included pregnancies with gestational age at delivery  $\geq 37$  and <42 weeks of gestation. Pregnancies with chromosomal or structural anomalies or suspected intrauterine infection were excluded. The hospital ethics committee approved the study protocol, and all patients gave written informed consent to participate in the study.

### *Data collection*

The following data were recorded upon enrollment: maternal age, ethnicity, body mass index (BMI), parity, smoking status, known chronic disease (i.e., hypertension, diabetes mellitus) and obstetric history. Gestational age was established by crown-rump length at first trimester.<sup>39</sup> Fetoplacental Doppler was obtained in the last 2 weeks of pregnancy and included: umbilical artery (UA) PI, calculated from three or more consecutive waveforms obtained from a free-floating portion of the umbilical cord at insonation angles of less than 30°; middle cerebral artery (MCA) PI at the proximal portion of the vessel; CPR, calculated as the ratio of MCA-PI to UA-PI;<sup>40</sup> and UtA-PI, calculated as the average PI of the right and left arteries.<sup>41</sup> At delivery, spontaneous onset of labor, route of delivery, gestational age, birth weight, birth weight centile, Apgar score, umbilical artery pH and placental pathology data were collected.

#### *Follow up and management*

All pregnancies with FGR diagnosis were monitored fortnightly with fetal growth evaluation, amniotic fluid assessment and Doppler measurements. The management of these pregnancies relied on a standardized protocol.<sup>5</sup> Indications for labor induction were as follows: 1) at  $\geq 26$  weeks' gestation: non-reassuring cardiotocography register and/or reversed ductus venosus (DV) diastolic flow 2) at  $\geq 30$  weeks' gestation, one or more of the following: UA reversed end diastolic volume, DV-PI  $\geq 95^{\text{th}}$  centile, DV absent diastolic flow 3) at  $\geq 34$  weeks' gestation: UA absent end diastolic volume 4) at  $\geq 37$  weeks' gestation, one or more of the following: estimated fetal weight  $< 3^{\text{rd}}$  centile, persistent (12 h apart) MCA-PI  $< 5^{\text{th}}$  centile or UA-PI  $> 95^{\text{th}}$  centile or CPR  $< 5^{\text{th}}$  centile, UtA-PI  $> 95^{\text{th}}$  centile 5) at  $\geq 40$  weeks' gestation, estimated fetal weight  $\geq 3^{\text{rd}}$  and  $< 10^{\text{th}}$  centile with normal Doppler parameters. In the first 3



scenarios, termination of pregnancy was by cesarean section, whereas in the next 2 by labor induction.

Pregnancies diagnosed with PE were classified as mild (to be terminated at  $\geq 37$  weeks) and severe (to be terminated at  $\geq 34$  weeks or before if applies). Severe PE was considered when it presented with one or more of the following<sup>38</sup>: blood pressure  $\geq 160$  mmHg systolic or  $\geq 110$  mmHg diastolic on two occasions at least 4 hours apart, thrombocytopenia ( $< 100000/\text{mm}^3$ ), impaired liver function (elevated blood concentrations of liver enzymes to twice normal concentration and/or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses), progressive renal insufficiency (serum creatinine concentration  $> 1.1$  mg/dl), pulmonary edema, new-onset cerebral or visual disturbances. Pregnancy termination was by labor induction or cesarean section upon obstetric indication.

Labor induction was achieved by hormonal cervical ripening with a slow-release prostaglandin E2 vaginal pessary (10mg) or mechanical with foley catheter. Oxytocin induction was indicated thereafter for failure of labor onset within 18 h. During the labor course, cesarean or operative vaginal delivery was indicated for non-reassuring fetal status, based on abnormal fetal heart rate tracing<sup>42</sup> and adverse fetal scalp blood pH during intrapartum monitoring.

#### *Placental evaluation*

Placental examinations adhered to a standard laboratory protocol.<sup>16</sup> Placentas were fixed in 10% buffered formalin. Trimmed placentas were weighted (after removal of the membranes, cord and any blood clots) and weight centiles were assigned based on gestational age-specific placenta weight charts.<sup>43</sup> After gross examination, samples

were taken for routine processing: three blocks containing a full thickness of normal-appearing placental parenchyma, two cross sections of umbilical cord, one rolled strip of membranes and samples from all visible lesions. Final slides were stained using hematoxylin and eosin. Diagnostics from pathology reports were classified according to Redline's classification following the 2014 Amsterdam Placental Workshop Group Consensus Statement.<sup>16</sup> Placental lesions were classified as vascular (maternal/fetal side), inflammatory-immune and other lesions.<sup>17</sup> Maternal and fetal vascular-stromal findings were classified as developmental, malperfusion or loss of integrity lesions. Inflammatory-immune processes included infectious (acute/chronic) and immune/idiopathic lesions. Other placental histopathological lesions were recorded separately.

To address reproducibility, a sample of 40 placentas (10 from each group) was selected randomly for re-evaluation, and pathologists were blinded to group classification and previous histologic diagnosis. An overall agreement of 87.5% was obtained by comparing the conventional placental pathology reports and the 40 placentas selected to assess reproducibility.

#### *Statistical analysis*

Data are presented as continuous or categorical variables. Differences in continuous and categorical variables were evaluated by Mann Whitney U, Pearson  $\chi^2$  or Fisher's exact test as appropriate. Multiple regression analysis was performed, and results were adjusted for confounding factors, including maternal race, pre-gestational BMI, smoking, nulliparity, gestational age at delivery, route of delivery and spontaneous onset of labor. A subanalysis dividing the population according to

gestational age at delivery term vs preterm was additionally performed (supplementary material). Probability values  $p < 0.05$  were considered statistically significant.

To investigate fetoplacental Doppler association with placental lesions, abnormal Doppler parameters were dichotomized into normal or abnormal when PI  $> 95^{\text{th}}$  centile for UtA and UA, or  $< 5^{\text{th}}$  centile for MCA and CPR. Logistic regression was used to calculate the adjusted odds ratios indicating the presence of placental lesions in the case of abnormal Doppler including all the pregnancies from the whole population. This analysis was performed also in the different groups of the study. Odds ratios were adjusted for maternal race, pre-gestational BMI, smoking, nulliparity, gestational age at delivery, route of delivery and spontaneous onset of labor. All statistical analyses were conducted using STATA 14 (StataCorp LLC, Texas, USA).

## Results

### *Study population*

A total of 608 pregnancies were included. Baseline characteristics, fetoplacental Doppler, and perinatal outcomes are shown in Table 1. Nulliparity and tobacco consumption were significantly higher in normotensive FGR pregnancies with a significantly lower maternal BMI. In contrast, preeclamptic patients with and without FGR had higher pre-gestational BMI and chronic comorbidities. With regards to the fetoplacental Doppler, UtA PI was significantly higher in all groups compared to controls, and the highest values were present in PE&FGR (Table 1). Additionally, the CPR z-score was significantly lower in groups with growth-restricted fetuses (with or without PE) compared to controls, especially in PE&FGR. As expected, all groups had an earlier gestational age at delivery compared to controls, less frequent spontaneous onset of labor and significantly increased prevalence of cesarean sections in pregnancies complicated by PE.

### *Placental evaluation and histopathological findings*

Placental weight and diameters were significantly lower in pregnancies with FGR compared to the other groups. Table 2 shows the morphological characteristics and histopathological lesions of the placenta and Figure 1 reveals the cumulative percentage of placental lesions observed among the different study groups. In normotensive FGR, vascular developmental lesions in the fetal side (chorangiosis mainly) were significantly higher in comparison to other groups. In both PE groups (with or without FGR), fetal side vascular lesions were less frequent compared to other groups. In addition, PE&FGR exhibited an increase of maternal side vascular lesions including 2 types, developmental (decidual arteriopathy mainly) and malperfusion. On the other hand, PE

with normally grown fetuses presented a nonsignificant increase of malperfusion lesions. Moreover, immune lesions (chronic villitis principally) were more prevalent in PE&FGR. Other immune lesions i.e. chronic histiocytic intervillitis presented with a low prevalence in the study cohort, it was observed in 1% of uncomplicated pregnancies, 1.1% of normotensive FGR and none of PE pregnancies. Infectious lesions were less frequent in all groups compared to controls particularly in PE&FGR.

A subanalysis according to gestational age at delivery showed similar patterns of placental lesions in association with PE and/or FGR, mainly in the preterm subpopulation (see supplemental material for details). Preterm cases of normotensive FGR were associated with maternal side malperfusion lesions (Table S2).

#### *Association of fetoplacental Doppler with placental findings*

As seen in Figure 2, all fetoplacental Doppler parameters (UtA, UA, MCA PI and CPR) were associated with maternal side vascular lesions without any significant association with fetal side vascular, inflammatory or other placental lesions. Actually, all pregnancies with fetal side developmental lesions in the placenta presented fetoplacental Doppler results within the normal ranges. Table 3 show adjusted odds ratios of each study group. Association with placental maternal side vascular lesions was mainly evident in normotensive FGR group with UtA or UA PI >95<sup>th</sup> centile and in controls with CPR < 5<sup>th</sup> centile.

## Discussion

The present study describes diverse patterns of placental lesions in a large well-characterized cohort displaying different clinical phenotypes of PE and FGR. Our data suggest that maternal PE is mainly associated with maternal side lesions, while FGR is associated with fetal side findings. Increased prevalence of immune processes was observed when both PE and FGR co-occur in the same pregnancy. In addition, we could demonstrate a significant association between placental maternal vascular lesions and fetoplacental Doppler, particularly in FGR complicated pregnancies.

Placentas from normotensive FGR pregnancies were significantly smaller and presented higher prevalence of fetal side developmental lesions where chorangiosis was the main finding. Chorangiosis, defined as extreme villous hypervascularity, was proposed to be a protective mechanism of the placenta against in utero hypoxia.<sup>44</sup> Despite being able to describe ‘typical’ vascular lesions in some cases of normotensive FGR (about 8-10%), a large proportion of cases displayed a placenta similar to controls. Previous studies described a variety of histopathological findings in FGR, ranging from morphologically unremarkable to delayed villous maturation<sup>45</sup>, pronounced maternal malperfusion lesions<sup>46</sup> or fetal villous changes.<sup>47</sup> This variability could be explained by the different phenotypes included in each study. Placental growth factor assessment in maternal plasma could help in detecting “placental” FGR.<sup>48</sup> In this study, we show that preterm FGR cases are associated with maternal side malperfusion lesions, whereas term cases showed the same prevalence as controls.

Pregnancies complicated by PE and FGR exhibited higher prevalence of maternal vascular lesions where malperfusion was mostly observed. PE association with

maternal malperfusion has been well-established<sup>15</sup> and correlated with the severity of PE.<sup>21,26,27,49</sup> Developmental lesions were also increased in PE&FGR. Our data suggest that decidual arteriopathy (the most common developmental finding) could represent a key insult in this subgroup of PE, causing maternal malperfusion that mediates uteroplacental ischemia.<sup>50</sup> However, malperfusion could also be originated from placental hypoperfusion due to maternal hemodynamic maladaptation which is most probably the mechanism underlying placental involvement in PE without FGR.<sup>51</sup> In addition, immune lesions were significantly higher in PE&FGR, mostly chronic villitis which has been linked to maternal immune response against the fetal allograft or an underlying infection.<sup>52</sup>

In addition, we observed a lower prevalence of infectious lesions in the cases groups, likely related to the lower rate of spontaneous onset of labor, as most PE and/or FGR pregnancies went through medically indicated delivery. Moreover, we noticed a high prevalence of vascular or inflammatory lesions in uncomplicated pregnancies which is consistent with the results of a recent study by Romero et al. demonstrating the association of these lesions with parturition without affecting the clinical course of the pregnancy.<sup>53</sup>

We also provide evidence of an association between placental lesions and fetoplacental Doppler. All the evaluated parameters (UtA, UA, MCA PI and CPR) showed a significant association with maternal side vascular findings. It has been previously proposed that abnormal Doppler parameters reflect the degree of placental insufficiency and are associated with placental findings indicative of placental underperfusion (without distinguishing maternal from fetal side lesions).<sup>54</sup> A higher rate of placental

vascular damage was reported in FGR cases with abnormal UtA<sup>55</sup>, UA<sup>56</sup> or both arteries PI.<sup>57</sup> In addition, abnormal CPR was associated with mural hypertrophy and maternal vascular underperfusion in FGR.<sup>58</sup> However, abnormal Doppler flow cannot be solely explained by altered uteroplacental histopathology.<sup>59–61</sup> On the other hand, FGR cases with normal fetoplacental Doppler exhibited higher prevalence of placental findings compared to uncomplicated pregnancies.<sup>35</sup> Additionally, UtA PI showed the ability to predict villous infarcts in PE.<sup>62</sup> Overall, fetoplacental Doppler seem to reflect placental vascular findings related to malperfusion. In the present study, with the use of a systematic classification for placental findings we demonstrate that abnormal fetoplacental Doppler is associated with maternal side vascular lesions and not with the fetal side or any other lesions.

Our study shows both strengths and limitations that worth mentioning. One of the strengths is the prospective design including well-characterized clinical phenotypes of PE and/or FGR, as well as uncomplicated pregnancies. Moreover, we used the most recent and comprehensive classification of placental findings<sup>17</sup> in accordance with the 2014 Amsterdam Placental Workshop Group criteria<sup>16</sup>, which established an agreed-upon protocol for sampling the placenta, and diagnostic criteria for placental lesions. As limitations, we acknowledge that pathologists were not completely blinded to the main diagnosis. Additionally, we have not considered any grading or staging of the lesions in our analysis, as our goal was focused on revealing the different placental patterns upon the presence/absence of specific placental findings. With regards to fetoplacental Doppler, we acknowledge the limited number of pregnancies with abnormal UA or MCA PI in some of the groups exhibiting appropriate for gestational age fetuses which



restrained the calculation of correspondent odds ratio. Furthermore, the analysis of angiogenic factors profile in these patients could be of interest in future research.

The placenta is an essential organ for understanding the most relevant obstetric complications. In conclusion, different placental histopathological lesions are associated with their corresponding clinical presentations, as placental maternal side lesions are mainly associated with maternal disease -PE-, whereas fetal side lesions are mainly involved in the fetal phenotype -FGR-. Fetoplacental Doppler parameters (UtA, UA, MCA PI and CPR) seem to be associated with placental maternal side lesions particularly in FGR, which reinforces the use of Doppler as a surrogate of placental insufficiency.

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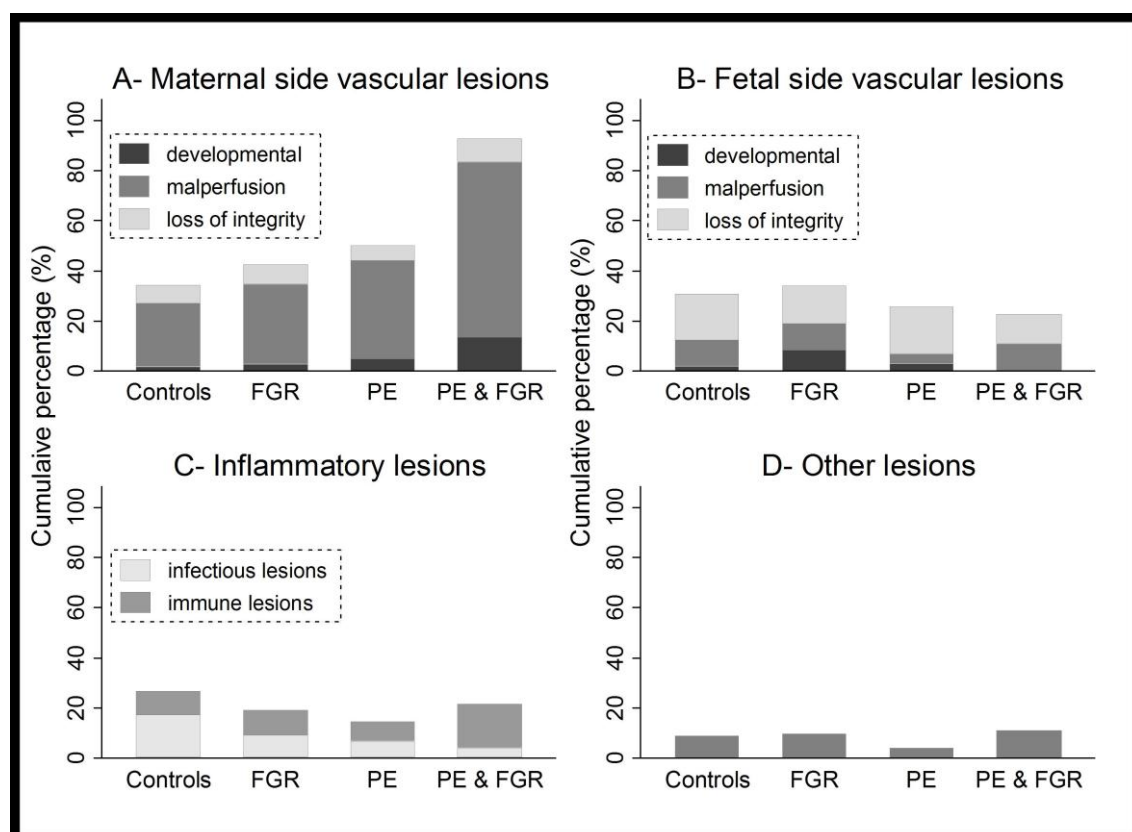


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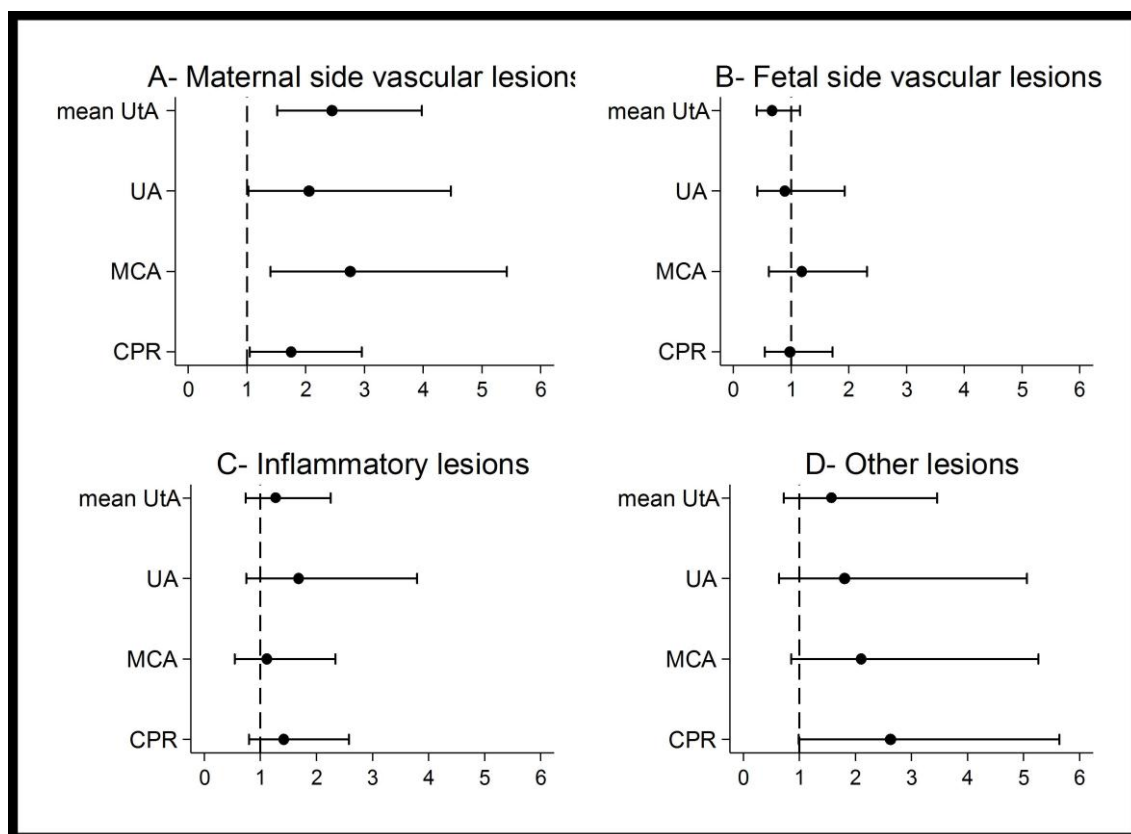
## Figure legends

**Figure 1.** Distribution of placental histopathological lesions among the study groups. Columns show cumulative percentage of placental lesions. FGR, fetal growth restriction; PE, preeclampsia.



**Figure 2.** Fetoplacental Doppler association with placental histopathological lesions.

Bars demonstrate adjusted odds ratio with 95% confidence interval. UtA, uterine arteries; UA, umbilical artery; MCA, middle cerebral artery; CPR, cerebroplacental ratio. Odds ratios were adjusted for maternal race, pre-gestational BMI, smoking, nulliparity, gestational age at delivery, route of delivery and spontaneous onset of labor.



**Tables****Table 1.** Clinical characteristics and perinatal outcomes of the study population.

	<b>Normotensive</b>	<b>Normotensive</b>	<b>Preeclampsia</b>	<b>Preeclampsia</b>
	<b>AGA</b>	<b>FGR</b>	<b>AGA</b>	<b>FGR</b>
	<b>N=202</b>	<b>N=184</b>	<b>N=102</b>	<b>N=120</b>
<i>Maternal characteristics</i>				
Age (years)	33.6 (30.5 – 36.5)	33.4 (29 – 36.4)	34.4 (31.4 – 37.1)†	35 (30.1 – 37.8)†
Body mass index (Kg/m <sup>2</sup> )	22.8 (20.5 – 25.3)	21.6 (19.8 – 23.4)*	25.8 (22.7 – 28.9)*†	23.8 (21.1 – 27.3)*†‡
Race				
White	131 (65.2)	140 (76.5)	50 (49)†	73 (60.8)
Latin-American	30 (14.9)	13 (7.1)	24 (23.5)*†	17 (14.2)‡
South Asian	24 (11.9)	23 (12.6)	20 (19.6)*	11 (9.2)‡
African	2 (1)	2 (1.1)	5 (4.9)	9 (7.5)*†
Others	14 (7)	5 (2.7)	3 (2.9)	10 (8.3)
Nulliparity	93 (46)	109 (60.6)*	55 (53.9)	81 (67.5)*‡
Smoking during pregnancy	23 (11.4)	48 (26.8)*	10 (9.8)†	19 (15.8)†
Chronic hypertension	4 (2)	4 (2.2)	19 (18.6)*†	14 (11.7)*†
Pre-gestational diabetes	2 (1)	5 (2.7)	17 (16.7)*†	4 (3.3)‡
<i>Fetoplacental Doppler before delivery</i>				

UtA-PI (z-score)	-0.17 (-1.1 – 0.79)	0.54 (-0.34 – 2)*	0.52 (-0.63 – 1.97)*	2.81 (1.92 – 3.5)*†‡
UA- PI (z-score)	-0.22 (-0.6 – 0.21)	0.32 (-0.17 – 0.96)*	0.05 (-0.45 – 0.38)*†	0.63 (0.14 – 1.9)*†‡
MCA-PI (z-score)	0.01 (-0.68 – 0.74)	-0.26 (-0.96 – 0.47)*	-0.32 (-0.75 – 0.46)	-1.15 (-2.11 – -0.35)*†‡
CPR (zscore)	-0.23 (-0.81 – 0.56)	-0.99 (-1.68 – -0.21)*	-0.48 (-1.23 – 0.31)†	-1.62 (-2.7 – 0.83)*†‡
<i>Perinatal outcomes</i>				
Spontaneous onset of labor	106 (52.5)	34 (18.5)*	7 (6.9)*†	7 (5.8)*
Cesarean section	67 (33.7)	84 (46.4)	70 (68.6)*†	84 (70.6)*†
Gestational age at delivery (weeks)	39 (35.7 – 40.1)	37.7 (37 – 39.4)*	37.1 (34.6 – 38)*†	34 (31.2 – 36.1)*†‡
Birthweight (g)	3020 (2510 – 3420)	2337 (1935 – 2613)*	2737 (2220 – 3155)†	1526 (1012 – 1945)*‡
Birth weight centile	38 (22 – 64)	1.5 (0 – 4.5)*	38 (17 – 83)†	0 (0 – 1)*‡
Male gender	110 (54.7)	97 (52.7)	53 (52)	67 (55.8)

APGAR 5 min <7	3 (1.5)	7 (3.8)	3 (2.9)	11 (9.3)*†
Fetal acidosis‡	8 (7.1)	11 (7.8)	7 (7.9)	10 (12.1)

Data are median (interquartile range) or n (percentage).

AGA, appropriate for gestational age; FGR, fetal growth restriction; UtA, uterine arteries; UA, umbilical artery;

MCA, middle cerebral artery; PI, pulsatility index; CPR, cerebroplacental ratio. ‡ Fetal acidosis was

defined as umbilical arterial cord blood pH <7.1.

\* p<0.05 by Mann-Whitney U, Pearson  $\chi^2$ , or Fisher's exact tests as appropriate, compared to controls.

† p<0.05 by Mann-Whitney U, Pearson  $\chi^2$ , or Fisher's exact tests as appropriate, compared to normotensive FGR.

‡ p<0.05 by Mann-Whitney U, Pearson  $\chi^2$ , or Fisher's exact tests as appropriate, compared to preeclampsia + AGA.

**Table 2.** Placental morphological characteristics and histopathological lesions among the study groups.

	<b>Normotensive AGA N=202</b>	<b>Normotensive FGR N=184</b>	<b>Preeclampsia AGA N=102</b>	<b>Preeclampsia FGR N=120</b>
<i>Morphological characteristics</i>				
Placental weight (g)	479 (402 – 540)	357 (292 – 425)*	489 (375 – 565)†	290 (220 – 358)*†‡
Placental weight <10th centile	18 (9)	72 (39.1)*	4 (4)†	37 (31.1)*‡
Placental weight <3rd centile	6 (3)	32 (17.4)*	0 (0)†	10 (8.4)*‡
Placental length (cm)	17 (15.5 – 18.8)	15.5 (14 – 17)*	17 (16 – 18)†	14 (12 – 15)*†‡
Placental breadth (cm)	15.5 (14 – 17)	14 (12 – 15.3)*	15 (14 – 16.5)†	11.8 (10 – 13.5)*†‡
Placental thickness (cm)	2.5 (2 – 3)	2 (1.5 – 2.5)*	2.5 (2 – 3)†	2.2 (2 – 3)
<i>Histopathological lesions</i>				
1. Vascular lesions				
Maternal side lesions	62 (30.7)	70 (38)	47 (46.1)	88 (73.3)*†‡
maldevelopment	3 (1.5)	5 (2.7)	5 (4.9)	16 (13.3)*†‡
malperfusion	51 (25.2)	58 (31.5)	40 (39.2)	84 (70)*†‡
loss of integrity	15 (7.4)	15 (8.2)	6 (5.9)	11 (9.2)
Fetal side lesions	57 (28.2)	57 (31)	23 (22.6)*	27 (22.5)*†
maldevelopment	4 (2)	15 (8.2)*	3 (2.9)	0 (0)†
malperfusion	21 (10.4)	19 (10.4)	4 (3.9)	13 (10.8)



loss of integrity	37 (18.3)	28 (15.2)	19 (18.6)	14 (11.7)*
Combined maternal and				
fetal side lesions	22 (11)	23 (12.6)	15 (14.7)	20 (16.7)
maldevelopment	0 (0)	0 (0)	0 (0)	0 (0)
malperfusion	7 (3.5)	10 (5.5)	3 (2.9)	8 (6.7)
loss of integrity	3 (1.5)	1 (0.6)	0 (0)	1 (0.8)
2.Inflammatory lesions				
Infectious lesions	35 (17.3)	17 (9.2)†	7 (6.9)†	5 (4.2)*
Immune lesions	19 (9.4)	18 (9.8)	8 (7.8)	21 (17.5)*†‡
3.Other lesions				
Massive perivillous				
fibrin(oid) deposition				
(maternal floor	5 (2.5)	7 (3.8)	1 (1)	2 (1.7)
infarction)				

Data are median (interquartile range) or n (percentage).

AGA, appropriate for gestational age; FGR, fetal growth restriction.

\*  $p < 0.05$  by linear or logistic regression as appropriate, compared to controls.

†  $p < 0.05$  by linear or logistic regression as appropriate, compared to normotensive FGR.

‡  $p < 0.05$  by linear or logistic regression as appropriate, compared to preeclampsia + AGA.

Results were adjusted for maternal race, pre-gestational BMI, smoking, nulliparity, gestational age at delivery, route of delivery and spontaneous onset of labor.

Combined maternal and fetal side lesions were considered when lesions in both sides were present in the same placenta.

**Table 3.** Fetoplacental Doppler association with maternal side vascular lesions in the placenta among the study groups.

	<b>Normotensive</b>	<b>Normotensive</b>	<b>Preeclampsia</b>	<b>Preeclampsia</b>
	<b>AGA</b>	<b>FGR</b>	<b>AGA</b>	<b>FGR</b>
	<b>N=202</b>	<b>N=184</b>	<b>N=102</b>	<b>N=120</b>
Uterine arteries	1.62	3.14	5.51	1.84
mean PI >95 <sup>th</sup> centile	(0.43 – 6.03)	(1.36 – 7.24)*	(0.72 – 41.91)	(0.63 – 5.38)
Umbilical artery PI		3.78		1.18
>95 <sup>th</sup> centile	NA	(1.01 – 14.15)*	NA	(0.34 – 4.15)
Middle cerebral		1.89	2.39	1.5
artery PI <5 <sup>th</sup> centile	NA	(0.57 – 6.24)	(0.19 – 30)	(0.48 – 4.66)
CPR <5 <sup>th</sup> centile	5.99	1.91	9.12	0.91
	(1.04 – 34.62)*	(0.79 – 4.62)	(0.87 – 96.03)	(0.34 – 2.46)

Data are adjusted odds ratio (95% confidence interval).

AGA, appropriate for gestational age; FGR, fetal growth restriction; NA: nonapplicable.

\* p<0.05 by logistic regression. Odds ratios were adjusted for maternal race, pre-gestational BMI, smoking, nulliparity, gestational age at delivery, route of delivery and spontaneous onset of labor.

When there were very few cases having abnormal fetoplacental Doppler the calculation was nonapplicable (NA).