Preeclampsia (PE) is a potentially life-threatening, systemic, hypertensive disorder affecting 3% to 5% of all pregnancies. Responsible for >60,000 maternal deaths each year,1 PE is also a leading cause of fetal/neonatal mortality and morbidity. Classically, PE has been defined as new-onset hypertension and proteinuria after 20 weeks of gestation. However, the clinical presentation of PE is highly variable among women, and diagnostic guidelines now include signs and symptoms that are reflective of disease in ≥1 organ systems (liver, kidney, blood, and brain).2-4 Apart from expectant management and delivery of the infant and the placenta, there currently exists no cure or effective treatments for PE.

The placenta is widely considered to be the central component of the PE disease process, and as it is not required after birth, this presents a unique opportunity to assess a clinically relevant tissue involved in a hypertensive pathology. Accordingly, numerous placental analyses have been conducted with the aim of identifying early detection markers or candidates for therapeutic intervention in PE. These studies have uncovered involvement of molecular pathways, such as oxidative stress and secretion,4-6 and many secreted factors with disrupted expression during PE have been investigated as candidate blood biomarkers of this pathology.7-10 However, the predictive power of these molecules demonstrate low sensitivity at clinically relevant false-positive rates7 and, therefore, are not presently recommended for use as screening tools for PE.11

We,1-14 and others,15,16 have proposed that this lack of robust biomarkers and effective treatments for PE is because of the multifactorial nature of this disease, a notion supported by considerable evidence within the human literature.17-21 Further support also exists in the numerous developed animal models of PE that recapitulate many of the human symptoms and pathologies because these are the result of a range of initial insults, involving disruptions in placental22,23 or maternal24 genes, or a predisposing baseline maternal hypertension.25 As such, past placental microarray, and even meta-analysis26,27 studies with small and highly selected patient cohorts, predominately assessed using a binary classification system (of PE versus control), do not accurately reflect the true clinical presentation of patients. Even the separation of women into early-onset (diagnosis before 34 weeks) and late-onset PE groups18,21...
still does not fully explain the heterogeneity observed in this disorder. Although these studies are likely uncovering valid information about PE disease, these findings are not applicable to the full range of PE patients and, thus, do not result in clinical progress in prediction and treatment. A more complete molecular understanding of PE, therefore, requires both a large broad sample set representing the high variation of patients seen in a clinical setting and an unbiased analysis.

As a first step toward class discovery of PE pathology, we performed an aggregated analysis of 7 previously published human PE placental microarray data sets\(^4,5,28–32\) using unbiased/unsupervised multivariate clustering techniques.\(^13\) Our methods, which improve on similar approaches used for the molecular subclassification of tumors in the oncology field,\(^33,34\) blindly selected to span multiple distinct clinical classification groups of non-PE and PE patients. Although the goal was to collect at least 15 samples per clinical group, based on power analysis (PowerAtlas\(^18\) and the Benjamini-Hocherg framework for multiple testing), this was not feasible for all groups.

### Statistical Analysis

Analysis of the clinical and histopathologic data was performed using Mann–Whitney–Wilcoxon tests, Fisher’s exact tests, Kruskal–Wallis rank-sum tests, and Pearson correlations in R 3.1.3, as appropriate, using the BioBank samples only. Detailed methods are presented in the online-only Data Supplement.

### Assembly of the Combined Data Set

To address our primary hypothesis that multiple molecular subclasses of PE exist in the human population, we assembled a large gene expression data set of human placenta samples for class discovery. From the Research Centre for Women’s and Infants’ Health BioBank, we collected 157 placenta samples (BioBank samples) with detailed clinical data from a range of hypertensive and normotensive states. To increase our sample size, the BioBank samples were then combined with the 7 previously published placental microarray data sets\(^4,5,28–32\) (Table S1 in the online-only Data Supplement) that we have previously analyzed in aggregate (Aggregate samples).\(^13\) The final combined data set contained 330 placentas (157 PE and 173 non-PE) and expression values for 14651 genes found in common across all original microarray platforms. Only the top quartile of genes (3663 genes; Table S2), demonstrating the highest degree of variability across all samples, was used for clustering.

### Clustering and Sample Distribution

Unsupervised multivariate clustering of the combined data set identified 5 patient clusters as the optimal number using the Bayesian Information Criterion. Visualization of these clusters by principal component analysis revealed 2 larger clusters (clusters 1 and 2) at the center of the plot with 3 smaller clusters (clusters 3–5) radiating away from them (Figure 1A). We did not observe any significant differential distribution of the original data sets/batches across the clusters (Table S3).

We first assessed the clusters for the inclusion of PE and non-PE clinical groups (Figure 1B). Cluster 1 contained mostly controls (46/60 BioBank samples) from both preterm (<34 weeks) and term deliveries (Figure 1C). Curiously, cluster 1 also contained some of the term and preterm PE samples with average-for-gestational-age infants. Cluster 2 was composed predominately of PE samples (50/56), mostly delivered preterm or term with small-for-gestational-age infants (Figure 1C), as well as a portion of the BioBank samples from women with chronic hypertension (CH) but without PE who delivered prematurely. Clusters 3 and 5 contained a mixture of PE and non-PE samples, whereas cluster 4 was mostly composed of preterm controls (12/14; Figure 1C). Our clustering results therefore imply the existence of at least 4 molecular-based PE subclasses (in clusters 1, 2, 3, and 5).

### Correlations Between Cluster Membership and Clinical Information

To assess potential relationships between recorded clinical data and cluster membership, correlative analysis was applied to available maternal, fetal, and placental parameters for the BioBank samples (Table 1, Tables S4–S7, and Figure S1).

Overall, cluster 1 samples, including those diagnosed with PE, demonstrated the most normal Doppler ultrasound studies and placental weights, leading to infants born at later gestational ages with the highest Apgar scores (Table 1, Table S4, Table S6, and Figure S1A). The preterm controls belonging to this cluster were generally those with gestational ages between 30 and 34 weeks (Figure S1A), delivered for reasons such as cholestasis of pregnancy or placental abruption. In comparison to the other groups, cluster 1 contained few fetuses diagnosed with coexisting intrauterine growth restriction (IUGR), and the lowest percentage of newborns requiring transfer to the neonatal intensive care unit after delivery (Table 1, Table S5, Table S7, and Figure S1B).
In contrast to cluster 1, the high rate of PE diagnosis (≈89%) in cluster 2 was strongly associated with low-weight placenta and abnormal Doppler ultrasound waveforms, with all infant birth weights below the 50th percentile (Table 1, Table S4, and Table S6). Additionally, most of the cluster 2 infants were born preterm by nonlaboring Cesarean section, often resulting in infant transfer to the neonatal intensive care unit (Table 1, Table S5, Table S7, and Figure S1A). PE disease appeared to be more severe in this cluster because it included women with the highest maternal blood pressures, proteinuria levels, and uric acid levels (Table 1, Table S4, and Table S6). Moreover, many samples also associated with IUGR and hemolysis, elevated liver enzymes, and low platelets syndrome were dispersed throughout this cluster (Table 1, Table S5, Table S7, and Figure S1B and S1C).

Cluster 3 samples were generally delivered between 30 and 37 weeks from older women of a non-Caucasian ethnicity (Table 1, Table S4–S7, and Figure S1A). Placental weights were dramatically reduced with narrower umbilical cords, especially among the PE patients (Table 1, Table S4, and Table S6). Additionally, a significant gradient of fetal weight restriction severity was observed in cluster 3 samples (Figure 2A), with the majority of those that plotted the furthest from cluster 1 by principal component analysis also diagnosed with coexisting IUGR (Figure 2A and Figure S1B).

Cluster 4 members were preterm controls from younger mothers delivered before 30 weeks with average-for-gestational-age infants, as well as a few large-for-gestational-age infants (Table 1, Table S4, Table S5, and Figure S1A). Most of these women went into spontaneous labor with some infants delivered by Cesarean section (Table 1 and Table S5). Additionally, accompanying clinical and pathology data reported signs of infection (predominately choriovitamnitis) in 10 out of 12 preterm control placenta in cluster 4 (Table 1, Table S5, and Figure S1D). This was in contrast to only 3 (out of 11) preterm controls belonging to cluster 1 that showed signs of infection, and these were found to plot on the border of cluster 1, near cluster 4, by principal component analysis (Figure S1D).

Cluster 5 consisted of samples from a range of gestational ages at delivery, placental and infant weights, and PE or non-PE diagnoses (Table 1, Table S4, Table S5, and Figure S1). No clinical variables were found to be statistically significant or clinically relevant in describing this molecular subclass.

Intracluster Maternal Differences Between PE and Non-PE Patients

Of the identified clusters, 4 (clusters 1, 2, 3, and 5) contained varying but significant proportions of samples with a PE diagnosis, suggesting that maternal factors may protect or promote PE development in each of these groups. To address this, we specifically compared the available prepregnancy maternal clinical information between the BioBank PE cases (including those with superimposed PE disease on CH) and non-PE cases (normotensive controls and patients with preexisting CH who did not develop PE) in each of these 4 clusters (Table S8).

Interestingly, all 14 PE patients in cluster 1 were either nulliparous (P=0.1253) or had experienced a prior hypertensive pregnancy (P<0.01; Table S8). Cluster 2 non-PE women almost exclusively had CH (P<0.01), whereas the PE patients demonstrated a trend toward higher maternal body mass indices (P=0.1246; Table S8). Surprisingly, in cluster 3, the 3 women...
without PE had all experienced a previous miscarriage and were all B blood type (Table S8). This was in contrast to the 8 cluster 3 PE subjects, none of whom had experienced a miscarriage (P < 0.01) and the majority of whom were A blood type (P < 0.05) (Table S7, and Table S8). Cluster 5 PE and non-PE patients revealed no remarkable maternal differences (Table S8).

Gene-Set Enrichment Analysis Compared With Cluster 1
To begin to characterize the different clusters at a molecular level, we applied gene-set enrichment analysis (GSEA) to the full combined set of Aggregate and BioBank samples. Given that cluster 1 appeared to be the healthiest group of placentas in our data set, we chose to perform this analysis comparing clusters 2 to 5 to this cluster (Figure 3 and Table S9).

In contrast to cluster 1, the PE-enriched cluster 2 demonstrated an over-representation of genes involved in hormone secretion, response to nutrient levels, response to hypoxia, and oxidoreductase (redox) activity (Figure 3 and Table S9).

Cluster 3 revealed an enrichment of numerous genes involved in immune and inflammatory responses, cytokine/interferon signaling, and response to stress and hypoxia (Figure 3 and Table S9). Additionally, of particular interest in cluster 3 were genes associated with allograft rejection and viral reproduction (Figure 3 and Table S9). Compared with cluster 1, including the other preterm controls, cluster 4 demonstrated

Table 1. Important Clinical Differences Across Clusters

<table>
<thead>
<tr>
<th>Continuous attribute, within cluster mean (SD)</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>32.6 (4.8)</td>
<td>33.8 (6.1)</td>
<td>35.9 (4.2)</td>
<td>29.2 (6.4)</td>
<td>34.8 (5.4)</td>
<td>0.01963</td>
</tr>
<tr>
<td>Mean uterine artery PI</td>
<td>1.23 (0.46)</td>
<td>1.81 (0.48)</td>
<td>1.65 (0.47)</td>
<td>1.16 (0.25)</td>
<td>1.79 (0.56)</td>
<td>0.03034</td>
</tr>
<tr>
<td>Mean umbilical artery PI</td>
<td>1.16 (0.37)</td>
<td>1.51 (0.42)</td>
<td>1.52 (0.55)</td>
<td>1.07 (0.12)</td>
<td>1.38 (0.17)</td>
<td>0.0001159</td>
</tr>
<tr>
<td>Max systolic pressure, mmHg</td>
<td>139 (25)</td>
<td>172 (18)</td>
<td>159 (20)</td>
<td>131 (15)</td>
<td>155 (30)</td>
<td>1.548e-10</td>
</tr>
<tr>
<td>Max diastolic pressure, mmHg</td>
<td>89 (15)</td>
<td>109 (11)</td>
<td>98 (13)</td>
<td>82 (11)</td>
<td>95 (16)</td>
<td>4.18e-11</td>
</tr>
<tr>
<td>Mode proteinuria level (dipstick)</td>
<td>+1.0 (1.2)</td>
<td>+2.6 (1.3)</td>
<td>+2.1 (0.9)</td>
<td>+0.6 (1.0)</td>
<td>+1.4 (1.4)</td>
<td>3.593e-07</td>
</tr>
<tr>
<td>GA at delivery, weeks</td>
<td>36 (4)</td>
<td>31 (3)</td>
<td>34 (4)</td>
<td>29 (4)</td>
<td>33 (4)</td>
<td>2.286e-10</td>
</tr>
<tr>
<td>Newborn weight z-score</td>
<td>−0.13 (1.01)</td>
<td>−1.33 (0.74)</td>
<td>−1.46 (0.89)</td>
<td>0.34 (0.95)</td>
<td>−0.85 (1.15)</td>
<td>3.683e-11</td>
</tr>
<tr>
<td>Placental weight z-score</td>
<td>−0.37 (0.99)</td>
<td>−1.25 (0.76)</td>
<td>−1.31 (1.16)</td>
<td>0.72 (1.37)</td>
<td>−0.98 (0.79)</td>
<td>2.423e-08</td>
</tr>
<tr>
<td>Cord diameter, cm</td>
<td>1.31 (0.38)</td>
<td>1.12 (0.34)</td>
<td>0.93 (0.31)</td>
<td>1.22 (0.26)</td>
<td>1.21 (0.27)</td>
<td>0.009658</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical attribute, percentage of cluster (n/N)*</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66.7 (38/57)</td>
<td>44.6 (25/56)</td>
<td>27.3 (3/11)</td>
<td>64.3 (9/14)</td>
<td>66.7 (10/15)</td>
</tr>
<tr>
<td>Black</td>
<td>8.8 (5/57)</td>
<td>23.2 (13/56)</td>
<td>36.4 (4/11)</td>
<td>14.3 (2/14)</td>
<td>0 (0/15)</td>
</tr>
<tr>
<td>Asian</td>
<td>17.5 (10/57)</td>
<td>21.4 (12/56)</td>
<td>27.3 (3/11)</td>
<td>7.1 (1/14)</td>
<td>20.0 (3/15)</td>
</tr>
<tr>
<td>East Indian</td>
<td>5.3 (3/57)</td>
<td>7.1 (4/56)</td>
<td>9.1 (1/11)</td>
<td>7.1 (1/14)</td>
<td>0 (0/15)</td>
</tr>
<tr>
<td>BMI &gt;25 kg/m²</td>
<td>37.3 (22/59)</td>
<td>66.7 (30/45)</td>
<td>44.4 (4/9)</td>
<td>45.5 (5/11)</td>
<td>40.0 (6/15)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>23.3 (14/60)</td>
<td>30.4 (17/56)</td>
<td>36.4 (4/11)</td>
<td>0 (0/14)</td>
<td>37.5 (6/16)</td>
</tr>
<tr>
<td>Preeclampsia diagnosis</td>
<td>23.3 (14/60)</td>
<td>89.3 (50/56)</td>
<td>72.7 (8/11)</td>
<td>7.1 (1/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>HELLP diagnosis</td>
<td>1.7 (1/60)</td>
<td>32.1 (18/56)</td>
<td>9.1 (1/11)</td>
<td>0 (0/14)</td>
<td>12.5 (2/16)</td>
</tr>
<tr>
<td>IUGR diagnosis</td>
<td>8.3 (5/60)</td>
<td>41.1 (23/56)</td>
<td>63.6 (7/11)</td>
<td>0 (0/14)</td>
<td>31.5 (5/16)</td>
</tr>
<tr>
<td>Chorioamnionitis diagnosis</td>
<td>6.7 (4/60)</td>
<td>0 (0/56)</td>
<td>0 (0/11)</td>
<td>71.4 (10/14)</td>
<td>12.5 (2/16)</td>
</tr>
<tr>
<td>Attempted vaginal delivery</td>
<td>50.0 (30/60)</td>
<td>30.4 (17/56)</td>
<td>9.1 (1/11)</td>
<td>100 (14/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>38.3 (23/60)</td>
<td>12.5 (7/56)</td>
<td>9.1 (1/11)</td>
<td>64.3 (9/14)</td>
<td>18.8 (3/16)</td>
</tr>
<tr>
<td>Delivery &lt;34 wk</td>
<td>28.3 (17/60)</td>
<td>78.6 (44/56)</td>
<td>36.4 (4/11)</td>
<td>85.7 (12/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>Male fetus</td>
<td>51.7 (31/60)</td>
<td>57.1 (32/56)</td>
<td>45.5 (5/11)</td>
<td>57.1 (8/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>AGA (10–90th percentile)</td>
<td>85.0 (51/60)</td>
<td>44.6 (25/56)</td>
<td>36.4 (4/11)</td>
<td>78.6 (11/14)</td>
<td>50.0 (8/16)</td>
</tr>
<tr>
<td>SGA (&lt;10th percentile)</td>
<td>11.7 (7/60)</td>
<td>55.4 (31/56)</td>
<td>63.6 (7/11)</td>
<td>0 (0/14)</td>
<td>50.0 (8/16)</td>
</tr>
<tr>
<td>NICU transfer</td>
<td>18.3 (11/60)</td>
<td>51.8 (29/56)</td>
<td>36.4 (4/11)</td>
<td>42.9 (6/14)</td>
<td>37.5 (6/16)</td>
</tr>
</tbody>
</table>

AGA indicates, average for gestational age; GA, gestational age; HELLP, hemolysis, elevated liver enzymes, low platelets; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; PI, pulsatility index; and SGA, small for gestational age.

*All available data were used; however, information was missing for some characteristics in some BioBank samples. Complete data are indicated by N = 60 for cluster 1, N = 56 for cluster 2, N = 11 for cluster 3, N = 14 for cluster 4, and N = 16 for cluster 5.
Evidence for 2 Subclasses of PE-IUGR in Clusters 2 and 3

Interestingly, a significant portion of both cluster 2 (19/56) and cluster 3 (5/11) BioBank samples had coexisting diagnoses of PE and IUGR. We therefore investigated these 2 PE-IUGR subclasses further to determine whether the clinical and gene expression differences identified between these groups corresponded to distinctions in placental histopathologic features (Table 2, Figure S2, and Table S10).

Cluster 2 PE-IUGR samples displayed increased rates of distal villous hypoplasia ($P$=0.078), placental infarctions ($P$<0.05), and syncytial knots ($P$<0.01) compared with the PE-IUGR samples in cluster 3 (Table 2, Figure S2A, and Table S10). In contrast, 3 of the 5 cluster 3 PE-IUGR placentas exhibited signs of massive perivillous fibrin deposition ($P$<0.01; Table 2, Figure S2B, and Table S10), a pathology feature associated with maternal antifetal rejection and not observed in any cluster 2 PE-IUGR samples. On the principal component analysis plot, these 3 samples were on the leading edge of cluster 3, likely driving the molecular formation of this cluster and demonstrated the highest expression of the known rejection marker, chemokine C-X-C motif ligand 10 (CXCL10) (Figure 2B). Interestingly, attempts at identifying signs of a viral infection in cluster 3 BioBank samples by quantitative polymerase chain reaction (qPCR) and by histological examination (Table S10) were all negative.

Investigation Into Cluster 5 Placentas

Given the enrichment of olfactory-related terms in samples from cluster 5, we hypothesized that this cluster may exist because of (confined placental) chromosomal abnormalities in these samples, leading to common changes in gene expression despite clinical differences. A comparison of clusters 2 to 5 to cluster 1 with GSEA for chromosome positional enrichments based on gene expression identified 91 statistically significant gains or losses of chromosome regions in cluster 5 samples at a false discovery rate $Q$ value of 0.05 (Table S11). Chromosomal differences were not observed to nearly the same extent (<8 regions at $Q$$<$0.05) in clusters 2 to 4 (Table S11).

To confirm these cluster 5 chromosomal abnormalities, we subjected 8 cluster 5 BioBank samples to array-based comparative genomic hybridization analysis compared with a pooled reference sample of 10 BioBank cluster 1 term controls. Gains in cluster 5 samples were confirmed on chromosomes 1, 6, 16, 17, and 22, with the greatest gains identified on chromosome 19 ($P$<0.05; Figure 4A). Significant losses were also noted on chromosomes 4, 5, 13, and 21 in cluster 5 samples ($P$<0.05; Figure 4B). The mean fold change observed on chromosome 19 in cluster 5 samples compared with the reference sample (1.05–1.10) suggests mosaicism in 10% to 20% of placental cells.

qPCR Confirmation of Discriminatory Genes

Our observation of multiple molecular clusters of placental samples indicates that past and future research on PE may need to be re-evaluated in this new context. Given that microarrays and other genome-wide gene expression analyses are expensive for the classification of samples, we next sought to identify a small panel of candidate markers with the capacity to discriminate between our observed placental clusters. We
therefore selected a panel of 12 genes with significant differential expression between the 5 full clusters, in addition to the frequently studied markers fms-like tyrosine kinase-1 (\(\text{FLT1}\)) and endoglin (\(\text{ENG}\)), for validation by qPCR (Table S12).

A total of 11 out of 14 genes, including \(\text{FLT1}\) and \(\text{ENG}\), revealed moderate to strong correlations between the qPCR and the microarray values (\(r=0.65–0.96\) and \(P<0.01\)) in a subset of 33 BioBank samples (Figure S3 and Table S12). Expectedly, the PE samples in cluster 2 demonstrated the highest levels of \(\text{FLT1}\) and \(\text{ENG}\) expression and could be easily distinguished from all the assessed non-PE samples using only these 2 genes (Figure 5A). This was in contrast to the PE cases belonging to clusters 1, 3, and 5, which exhibited expression levels closer to non-PE placentas and were consequently poorly identified (Figure 5A). Furthermore, the few non-PE samples with elevated \(\text{FLT1}\) and \(\text{ENG}\) were from women with CH (Table S12).

The remaining 9 genes with correlating qPCR values were then assessed for their ability to discriminate between the 5 clusters using machine learning classification methods (Figure 5B). Cluster 1, 2, 3, and 4 samples were predominately assigned correctly (area under the curve: 0.965, 0.86,
Subclasses of Preeclampsia

Table 2. Important Histological Differences Between 19 Cluster 2 and 5 Cluster 3 PE-IUGR Samples

<table>
<thead>
<tr>
<th>Histological Attribute</th>
<th>Percentage of Group (n/N)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal villous hypoplasia</td>
<td>84.2 (16/19)</td>
<td>0.07849</td>
</tr>
<tr>
<td>Placental infarction</td>
<td>68.4 (13/19)</td>
<td>0.01087</td>
</tr>
<tr>
<td>Syncytial knots</td>
<td>89.5 (17/19)</td>
<td>0.006494</td>
</tr>
<tr>
<td>Massive perivillous fibrin deposition</td>
<td>0 (0/19)</td>
<td>0.004941</td>
</tr>
</tbody>
</table>

IUGR indicates intrauterine growth restriction; and PE, preeclampsia.

Discussion

Although years of research have identified molecular and histopathologic features enriched in placentas affected by PE, a large portion of patients do not share these characteristics and markers, thereby confounding their clinical utility for this disease.3 Based on the diversity of clinical attributes and animal models, we hypothesized that the application of class discovery methods to a large cohort microarray data set of placentas would allow for the identification of novel PE subclasses with distinct pathophysiology and influence of maternal factors.

Prior studies have revealed the existence of a late-onset (>34 weeks) PE pathology that is associated with a milder presentation of disease and no IUGR.21 Consistent with this literature, we observed that PE cases in cluster 1 were dominated by placentas from term and near-term delivery of average-for-gestational-age infants, with known maternal risk factors of nulliparity or a prior hypertensive pregnancy.18 Given that these placentas appear molecularly and anatomically normal, PE development in cluster 1 is likely driven by underlying maternal cardiovascular disease susceptibility in these...
subjects (ie, a “maternal” PE), either because of common risk factors or persistent endothelial damage from a previous pregnancy. Therefore, the acquisition of maternal samples, such as endothelial cells or plasma, will be required to comprehend the PE pathology observed in this subclass.

The more severe early onset (<34 weeks) form of PE is linked to IUGR and other signs of systemic maternal pathology, such as hemolysis, elevated liver enzymes, low platelets syndrome. Samples belonging to cluster 2 were highly enriched in PE, demonstrating elevated levels of known markers (FLT1 and ENG), smaller placental weights, early deliveries, and coexisting diagnoses of IUGR or hemolysis, low platelets. Histological examination of PE-IUGR samples from this cluster revealed signs of distal villous hypoplasia, placental infarctions, and syncytial knots, whereas GSEA identified enrichment of hypoxia, response to nutrients, and secretion ontologies, all of which have been previously reported in the analysis of PE. This supports a PE pathogenesis arising from a placental origin (ie, a classic, “canonical” PE; Figure 6).

However, given that cluster 2 is a large cluster, still exhibiting heterogeneity in disease severity and clinical outcomes, we are currently investigating these placenta samples further to uncover subclass-specific DNA methylation and histopathology patterns.

A novel finding of our study was the identification of another molecular group of PE samples in cluster 3 with a severe form of the pathology, including IUGR. Interestingly, although these placenta were associated with poor fetal outcomes, similar to cluster 2, the observed maternal parameters of disease severity, such as blood pressure and proteinuria levels, were not as dramatically increased in this cluster. Additionally, GSEA and histopathologic analysis of samples in cluster 3 identified enriched expression of immune response genes and poor maternal tolerance of the feto-placental unit, in addition to elevated levels of CXCL10, a marker of rejected organs. These findings, in combination with negative results for PE-associated viruses, favor an interpretation of cluster 3 as a maternal–fetal incompatibility coupled with a poor maternal response (ie, an “immunologic” PE; Figure 6).

Furthermore, an interesting correlate in our clusters, particularly in cluster 3, was maternal blood type and pregnancy history to the presence or absence of a PE diagnosis. Blood type A, common in cluster 3 PE patients, has been associated with an increase in inflammatory markers and coexisting events of small-for-gestational-age infants and PE. Conversely, blood type B, observed in all 3 non-PE subjects in cluster 3, has not been linked to this increased risk for PE, and thus may be immunologically protective, or at least neutral, toward the development of symptoms in the mother. Further investigation into this relationship will require matched placental and maternal samples to assess differences in MHC alleles and changes in immune cell activity. Additionally, although the observation of a previous miscarriage in all non-PE cluster 3 subjects and none of the cluster 3 PE subjects is certainly of...
interest, it is difficult to interpret without complete pregnancy history information, particularly concerning partner changes between pregnancies,\(^7\) which unfortunately was not available in this study.

An important consideration for future research in this field is the use of preterm controls. Within our data set, early preterm control placentas (<30 weeks) uniquely generated cluster 4. Clinically, these were predominately recorded as exhibiting signs of infection, mostly chorioamnionitis (Figure 6). Molecula- rly, cluster 4 demonstrated an over-representation of genes associated with development, because of their young age, and damage, because of this active infection. Although some previous PE studies have employed preterm controls for gestational age matching, others have used term placentas to eliminate confounding molecular changes caused by preterm pathologies. In our study, by comparing all samples together, we note that there is a significantly larger gene expression difference between the similarly aged preterm controls and PE samples than between the term controls and PE samples. Intriguingly, this may suggest that preterm PE samples may have prematurely aged giving them more molecular similarity to term controls. Regardless, consideration concerning appropriate experimental design and caution in data interpretation is required.

Finally, the increased power gained from the addition of the BioBank samples to the Aggregate samples led to the identification of cluster 5. This cluster contained a mixture of non-PE and PE samples with no differential enrichment of maternal or fetal attributes. However, we observed significant gains (on chromosomes 1, 6, 16, 17, 19, and 22) and losses (on chromosomes 4, 5, 13, and 21) in this cluster by both gene expression and array-based comparative genomic hybridization. Interestingly, these chromosomal abnormalities are frequently observed in cancer\(^44,45\) and, therefore, imply possible biological significance associated with increased invasion and proliferation that could benefit a PE placenta. Alternatively, these chromosomal anomalies may be a common, but confined, occurrence, and their sporadic detection may be because of frequent undersampling of this large organ, a situation improved by the BioBank’s strategy of biopsying 4 sample sites per placenta. Furthermore, our qPCR assessment of cluster membership could not predict cluster 5 but instead classified these samples into clusters 1 and 2, where they appeared to match similar clinical outcomes as bona fide members of these groups. This indicates that gene expression changes because of chromosomal abnormalities are likely in addition to changes in gene expression caused by disease (Figure 6). Future efforts should be directed toward determining the frequency of mosaicism in the human placenta and its possible aggravating or protective role in pathologies.

An additional significant finding of our current study was that expression differences between \textit{LIMCH1}, \textit{FSTL3}, and \textit{TAP1} genes were sufficient for discerning between placentas belonging to clusters 1, 2, 3, and 4 by qPCR. \textit{LIMCH1} has been shown to be involved in the organization of the actin cytoskeleton,
gene transcription, and RNA processing. FLT3, more highly enriched in the PE placentas than FLT1 or ENG, is an inhibitor of activin A and has been previously found to be elevated in PE and in response to hypoxia. TAP1, specifically upregulated in the immune-associated clusters, is involved in antigen presentation and HLA expression on the cell surface. As such, this small qPCR panel is a simple and convenient research tool for the subclassification of PE placentas into “maternal”, “canonical”, and “immunologic” groups. Further validation of this panel is a future direction.

Finally, an important observation in our study for the general field of CH was the identification of CH samples without preeclampsia in all PE-enriched clusters (1, 2, 3 and 5), with some even demonstrating elevated FLT1 and ENG. Although it is possible that several of these non-PE CH samples may be diagnosed as PE under the new broader guidelines, it is also likely that maternal factors can act to protect or exacerbate the transition to PE from a CH state. As such, analysis of maternal samples may yield biomarkers to predict PE development in CH women and distinguish between a diagnosis of PE and CH. Additionally, our observation of multiple non-PE preterm labor and PE-IUGR subclasses indicates that class discovery analysis of a larger focused set of samples could allow for further comprehension of these and other pathologies of pregnancy, such as gestational diabetes mellitus.

Although this study represents substantial progress toward understanding PE disease, it is not without limitations. Our results are dependent on the reliability of the microarray data collected in the 7 other used studies, as well as the assumption that biases in their initial sample selection, for example in ethnicity and gestational age, did not have a significant impact on the bioinformatic aggregation of the studies and the resulting combined data set. Furthermore, although we think that the considerable molecular, clinical, and histopathologic distinctions observed across the clusters strongly implies that different originating insults are responsible for the presentation of PE in the different subclasses, this of course cannot be confirmed using end-stage placental tissue. Future research will therefore require the identification or development of cellular and animal models representing each of our proposed potential etiologies of PE.

Perspectives
Overall, this work provides significant insight into the placental heterogeneity observed in preeclampsia. This knowledge of the existence of PE subclasses will be key for the generation of robust biomarkers capable of identifying all of these groups early in gestation and allow for the development and implementation of etiology-based treatments aimed at specific subclasses of this disorder. As in other fields of medicine, such as oncology, this personalized medicine approach will no doubt improve short- and long-term health outcomes for both the mother and the child. Moreover, a method similar to ours could be applied to many human diseases to remove confounding from the assessment of clinically similar samples with different molecular causes.

Acknowledgments
We thank the donors and Research Centre for Women’s and Infants’ Health (RCWHH) BioBank for the human specimens used in this study. We also thank Dr Gary Bader for bioinformatic assistance, the 3D CFI Centre at the University of Toronto for access to qPCR machinery and Sean Froese for technical assistance.

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Disclosures
None.

References
Novelty and Significance

What Is New?

- With 330 samples, we have performed the largest placental microarray study of preeclampsia to date.
- An unbiased assessment of this data revealed multiple molecular subclasses of preeclampsia with distinct clinical, ontological, and histopathologic features and maternal influences.
- An identified 3 gene quantitative polymerase chain reaction panel provides a simple research strategy for classifying preeclamptic placentas.

What Is Relevant?

- The discovery of these preeclampsia subclasses opens opportunities for personalized medicine in patient stratification and advancement of research in predicting and treating these diverse pathophysiology.

Summary

By applying unsupervised clustering techniques to a large cohort of preeclamptic placentas, we have substantially improved our understanding of this heterogeneous hypertensive disorder.
Unsupervised Placental Gene Expression Profiling Identifies Clinically Relevant Subclasses of Human Preeclampsia
Katherine Leavey, Samantha J. Benton, David Grynspan, John C. Kingdom, Shannon A. Bainbridge and Brian J. Cox

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http://hyper.ahajournals.org/content/68/1/137

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2016/05/09/HYPERTENSIONAHA.116.07293.DC1
ONLINE SUPPLEMENT

Unsupervised Placental Gene Expression Profiling Identifies Clinically Relevant Subclasses of Human Preeclampsia

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METHODS

Clinical definitions and criteria
At the time of sample collection and purchase, PE was defined as the onset of systolic pressure \( \geq 140 \text{ mmHg} \) and/or diastolic pressure \( \geq 90 \text{ mmHg} \) after the 20\textsuperscript{th} week of gestation, accompanied by proteinuria (greater than 300 mg protein/day, or greater \( \geq 2+ \) by dipstick) [1]. Chronic maternal hypertension was defined as systolic pressure \( \geq 140 \text{ mmHg} \) and/or sustained diastolic \( \geq 90 \text{ mmHg} \) before the 20\textsuperscript{th} week of gestation. Within these groups, there was an approximately balanced representation of fetal sex and co-morbidities of preterm (< 34 weeks gestation) and small-for-gestational-age infants (SGA; neonatal birth weight < 10\textsuperscript{th} percentile for gestational age and sex). Patients with diabetes (pre-existing or gestational), sickle cell anemia and/or morbid obesity (BMI \( \geq 40 \)) were excluded, and all samples came from singleton pregnancies. Some samples were also associated with HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets (thrombocytopenia, <100,000/ul)) and/or intrauterine growth restriction (IUGR; SGA neonate with abnormal umbilical artery Doppler waveforms and/or signs of placental insufficiency and/or abnormal placental function markers prior to delivery).

Microarrays
Placental sampling was performed by the BioBank (http://biobank.lunenfeld.ca/), utilizing a systematic procedure in which four tissue biopsies (one sample/quadrant, excluding the chorionic plate) are collected per placenta, rinsed in PBS to remove contaminating maternal blood, pooled, snap-frozen in liquid nitrogen, and crushed into a powder. mRNA was extracted from each of these placental samples using Trizol and RNAeasy spin columns, quality controlled on an Agilent Bioanalyzer, and sent to the Princess Margaret Genomics Centre (Toronto, Canada) for hybridization against Human Gene 1.0 ST Array chips (Affymetrix). This microarray data is available from the Gene Expression Omnibus (GEO) database under the accession number GSE75010.

Assembly and clustering of the combined data set
The 157 BioBank microarray .CEL files (“BioBank” samples) were processed, normalized, and converted into log2 values in R 3.0.1 using the Affy library. In order to increase the sample size, as well as study placentas from several geographic regions, these samples were merged with seven previously published data sets (Table S1) (“Aggregate” samples) using the virtualArray package [2], which employs empirical Bayes methods of normalization and batch correction. For this step, the BioBank files were split into three random groups, as virtualArray cannot handle data sets as large as 157 samples. This combined set of BioBank and Aggregate samples was then unbiasedly assessed as previously described [3]. Briefly, the data set was filtered for genes with variances in the top quartile, and subjected to unsupervised multivariate model-based clustering, using the mclust package [4], as well as principal component analysis (PCA), using the rgl library. The center of cluster 1 by PCA was utilized as being representative of “normal” for the identification of a gradient of fetal weight z-scores in cluster 3 and sample selection for aCGH, while the center of cluster 2 was utilized as being representative of a classic PE placenta for the assessment of CXCL10 expression in cluster 3 samples.

The random splitting of the BioBank samples into three groups, followed by merging by virtualArray and clustering, was performed ten times to very similar results, and the final clusters
used for downstream analysis were representative, and contained an unbiased distribution of samples from the different data sets/batches (Table S3). Also, while a reduction in gene number was required for clustering by *mclust*, a possible limitation of using the top quartile of variable genes is that these may include genes with a high degree of inter-individual variability, independent of clinical features.

**Organization of the clinical information**

The BioBank samples were accompanied by a significant amount of maternal and fetal clinical information (GA, ethnicity, fetal sex, pregnancy history, method of delivery, etc.), as well as details about the placentas themselves (weight, dimensions, and umbilical cord information). While most clinical attributes were known for all BioBank samples, others (such as blood work, paternal ethnicity, and Doppler ultrasound data) were not complete. This clinical data was merged with the gene expression data set in R. Covariates were converted (if necessary) to either a continuous numeric or a categorical variable for analysis. In cases where multiple measurements over pregnancy were available per patient (ex. blood pressure or Doppler ultrasound pulsatility index), the mean, maximum, minimum, and/or mode value across gestation was calculated, as appropriate. Placental weight z-scores were computed based on normal weight charts for male and female fetuses [5], and the placental surface areas were calculated from the placental dimensions based on the surface area of an ellipsoid. Blood work results obtained on the day of delivery were removed as to avoid potential confounding with the effect of labor or C-section surgery. While the Aggregate data was included in the initial clustering and PCA visualization for statistical power, all detailed clinical phenotyping of the clusters was performed on the BioBank samples only, as these were the samples where this information was available.

**Gene set enrichment analysis (GSEA)**

Each of the complete clusters 2-5 were compared individually to the “normal” cluster 1 using the Molecular Signatures Database (MsigDB) associated with the Gene-Set Enrichment Analysis (GSEA) software v2.1.0 [6], similar to previously described [3]. Briefly, all GO gene sets (v4.0), Canonical Pathways gene sets (v5.0), Hallmark gene sets (v5.0), and Positional gene sets (v5.0) with 10–1000 members were assessed against a background model of the 14,651 genes found in common across all original microarray platforms. The recommended number of permutations (1000) was performed with the less stringent (gene set) permutation type. Over-represented GO ontologies were visualized in Cytoscape v2.8.3 using the two-color Enrichment Map plugin [7], with a raw p-value cutoff of 0.01, a corrected false discovery rate (FDR) q-value cutoff of 0.25, and an overlap coefficient of 0.5. Nodes were re-colored to reflect the cluster in question, and networks of related ontologies were circled and assigned a group label.

**Placental histology**

The PE-IUGR BioBank placental samples from cluster 2 (19/56) and cluster 3 (5/11) were assessed by routine histology. Placental tissue biopsies and corresponding placental pathology reports were purchased through the RCWIH BioBank. Tissue biopsies (4-5) were excised from the central portion of the placental disc, fixed in formalin, and embedded in paraffin wax. Tissue blocks were sectioned (5 µm thick) and sections were stained with hematoxylin and eosin using standard laboratory protocol. High-resolution digital images of the stained sections were taken (Aperio® ScanScope) and stored on external hard drives. A single experienced perinatal pathologist, masked to microarray results and clinical outcomes, examined
the digital images and determined the presence or absence of significant pathological lesions (Table S10), defined according to published literature [8-10]. Gross anatomy (e.g. placental weight, umbilical cord length, etc.) was obtained from the placental pathology reports accompanying the BioBank tissue samples. Several microscopic lesions were also obtained from the BioBank reports (e.g. placental infarction, chronic deciduitis, etc.) as the biopsies were collected from areas where tissue appeared grossly normal and only included villous parenchyma (i.e. maternal decidua was not sampled).

**Array-based comparative genomic hybridization (aCGH)**

DNA was isolated (Promega Wizard® Genomic DNA Purification Kit) for the eight cluster 5 BioBank samples that plotted the furthest from the center of cluster 1 by PCA, and subjected to array-based comparative genomic hybridization (aCGH) analysis (Princess Margaret Genomics Centre (Toronto, Canada); Agilent Human 8x60K Array), compared to a pooled reference sample of the ten cluster 1 BioBank controls that were closest to the center of cluster 1. The raw aCGH data was background-subtracted and normalized using the CGHnorm package in R, and the results were analyzed and visualized using the KCsmart library [11], with a kernel width of 6Mb, a median probe distance of 41Kb, and 1000 permutations. The mean fold changes across the probes on chromosome 19 in cluster 5 samples versus the pooled reference sample were calculated and utilized in an algebraic formula ((1.5 fold change x estimated portion of cells with a trisomy) + (1 fold change x (1 – estimated portion of cells with a trisomy)) = mean fold change) to estimate the number of biopsied placental cells with a potential trisomy.

**Quantitative polymerase chain reaction (qPCR)**

Ten cluster-by-cluster comparisons were performed using the limma package in R [12] in order to determine the top differentially expression genes between the complete clusters. From these, 12 genes were selected (2 genes for comparisons involving cluster 1, due to anticipated difficulties separating this cluster from all four bordering clusters, and 1 gene for the remaining comparisons). Human TaqMan primer/probes sets were purchased from Life Technologies for SNX10 (Hs00203362_m1), VPS54 (Hs00212957_m1), MAN1C1 (Hs00220595_m1), TPBG (Hs00272649_s1), TAPI (Hs00388675_m1), LIMCH1 (Hs00405524_m1), FSTL3 (Hs00610505_m1), MTIF (Hs00744661_sH), MORN3 (Hs00900107_g1), PIK3CB (Hs00927728_m1), SQRDL (Hs01126963_m1), and METTL18 (Hs01851858_s1). Primer/probes sets were also obtained for two known PE markers, FLT1 (Hs01052961_m1) and ENG (Hs00923996_m1), and two reference genes, ACTB (Hs99999903_m1) and HPRT1 (Hs99999909_m1), as well as isolated RNA from a healthy placenta for use as a consistent external reference sample across all plates (catalog number AM7950). Twelve cluster 1 BioBank samples, eight cluster 2 samples, five cluster 3 samples, five cluster 4 samples, and five cluster 5 samples were randomly selected for qPCR using the sample function in R. RNA for each of these 36 samples (35 BioBank and 1 reference) was converted into complementary DNA (cDNA) using reagents purchased from Life Technologies (catalog numbers 48190011 and 18064014), Thermo Fisher Scientific Biosciences (material number R0192), and New England BioLabs (product codes M0297S1 and M0303S1). For two cluster 1 samples, sufficiently concentrated cDNA could not be obtained, and these were consequently excluded from further analysis. Plates were loaded with 4.5µl diluted cDNA, 0.5µl primer/probe, and 5.0µl TaqMan Universal PCR Master Mix (Life Technologies, catalog number 4304437) by an Eppendorf epMotion® 5070 automated pipetting system. The qPCR reaction was performed by a Life
Technologies QuantStudio™ 7 Flex Real-Time PCR System using default TaqMan cycling conditions (an initial denaturation step of 10 minutes at 95°C; and 40 cycles of 95°C (15 seconds) and 60°C (1 minute)). Samples were run in triplicate and averaged for analysis.

Mean C_T values were initially analyzed by the comparative C_T method [13] in order to obtain a fold change expression difference for each gene of interest in each sample of interest compared to the reference sample. The data was then loaded into R 3.1.3, log2 transformed, and compared to the log2 microarray results by Pearson's product moment correlations. qPCR values for significantly correlating genes were assessed for their necessity and ability to differentiate between the clusters using the WEKA machine learning software package [14]. Receiver operator characteristic (ROC) curves were produced by Random Forest classification methods with 1000 trees and 10-fold cross-validation, while attribute selection for the separation of clusters 1-4 was performed by an exhaustive search with Correlation-based Feature Subset Selection, still using the log2 values obtained by the comparative C_T method. Raw differences in the mean C_T values for the genes identified by attribute selection in the samples of interest were then assessed by J48 methods with 10-fold cross-validation in WEKA to generate a decision tree for the classification of samples into clusters 1, 2, 3, and 4.

qPCR was also performed in three cluster 3 samples to assess the possible presence of cytomegalovirus (UL132 gene, Pa03453400_s1), human papillomavirus 16 (E1 gene, Pa03453396_s1), and/or Epstein–Barr virus (IR1 gene, Pa03453399_s1). These viruses were chosen as they have been shown to be capable of infecting trophoblasts and have been associated with PE [15-17].

**Study Approval**

Ethics approval for this study was granted from the Research Ethics Boards of Mount Sinai Hospital (#13-0211-E), the University of Toronto (#29435), and the Ottawa Health Science Network (#2011623-01H). All women provided written informed consent for the collection of biological specimens and medical information.
REFERENCES

Table S1. The seven previously published PE microarray data sets used in this study.

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<th>GEO ID</th>
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<th>Controls</th>
<th>Total Samples</th>
<th>PE definition</th>
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<td>GSE30186</td>
<td>Illumina HumanHT-12 V4.0 expression beadchip</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>Maternal systolic and diastolic blood pressure $&gt;140/90$ mm Hg on at least two occasions separated by 6 h after 20 weeks of gestation, with urinary protein $&gt;2+$ on dipstick, or $&gt;0.3$ g/day.</td>
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<td>GSE10588</td>
<td>AGI Human Genome Survey Microarray Version 2</td>
<td>17</td>
<td>26</td>
<td>43</td>
<td>Blood pressure (BP) of at least 160 mmHg (systolic) and/or 110 mmHg (diastolic), with proteinuria $\geq 2+$ on dipstick, measured on at least two occasions 6 h apart while the patient was on bed rest, or hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, after the 20th week of gestation</td>
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<td>GSE24129</td>
<td>Affymetrix Human Gene 1.0 ST Array</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td>Blood pressure of higher than 140/90 mmHg, with proteinuria of more than 0.3 g in a 24 hour collection. Systolic pressure $\geq 140$ mmHg, diastolic pressure $\geq 90$ mmHg, and proteinuria $\geq 0.3$ g in a 24 hours collection</td>
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<td>37</td>
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<td>12</td>
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<td>8</td>
<td>16</td>
<td>New onset hypertension (diastolic BP of $\geq 90$ mmHg, based on the average of at least two measurements, taken using the same arm) after 20 weeks with proteinuria ($\geq 0.3$ g/d in a 24-hour urine collection or $\geq 30$ mg/mmol urinary creatinine in a spot (random) urine sample) or one/more adverse maternal condition(s)</td>
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TOTAL: 77 96 173
Table S3. Contribution of each data set/batch to the clusters. For aggregation, the BioBank samples were split into three random groups. There was no significant differential distribution of the batches across the clusters (p-value ≈ 0.74).

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<td>2.16 (0.66)</td>
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<td>2.21 (0.99)</td>
<td>0.1185</td>
</tr>
<tr>
<td>Mean umbilical artery PI†</td>
<td>1.16 (0.37)</td>
<td>1.51 (0.42)</td>
<td>1.52 (0.55)</td>
<td>1.07 (0.12)</td>
<td>1.38 (0.17)</td>
<td>0.0001159</td>
</tr>
<tr>
<td>Max umbilical artery PI†</td>
<td>1.29 (0.43)</td>
<td>1.67 (0.51)</td>
<td>1.69 (0.48)</td>
<td>1.13 (0.12)</td>
<td>1.50 (0.25)</td>
<td>0.000363</td>
</tr>
<tr>
<td>Mean middle cerebral artery PI†</td>
<td>1.76 (0.39)</td>
<td>1.53 (0.24)</td>
<td>1.49 (0.12)</td>
<td>1.90 (0.48)</td>
<td>1.67 (0.42)</td>
<td>0.03249</td>
</tr>
<tr>
<td>Min middle cerebral artery PI†</td>
<td>1.63 (0.39)</td>
<td>1.34 (0.30)</td>
<td>1.28 (0.12)</td>
<td>1.75 (0.58)</td>
<td>1.43 (0.38)</td>
<td>0.01206</td>
</tr>
<tr>
<td>Mean MCA peak systolic velocity (cm/sec)</td>
<td>46.6 (11.3)</td>
<td>48.3 (10.0)</td>
<td>45.9 (14.2)</td>
<td>30.0 (7.7)</td>
<td>49.4 (9.6)</td>
<td>0.029</td>
</tr>
<tr>
<td>Max MCA peak systolic velocity (cm/sec)</td>
<td>52.5 (16.2)</td>
<td>54.7 (12.1)</td>
<td>56.6 (8.5)</td>
<td>35.2 (14.1)</td>
<td>53.4 (11.1)</td>
<td>0.1061</td>
</tr>
<tr>
<td>Mean biophysical profile score (/10)</td>
<td>7.73 (0.64)</td>
<td>7.58 (0.79)</td>
<td>7.08 (0.92)</td>
<td>6.64 (1.69)</td>
<td>7.44 (0.88)</td>
<td>0.1269</td>
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<tr>
<td>Min biophysical profile score (/10)</td>
<td>7.43 (1.32)</td>
<td>7.11 (1.32)</td>
<td>6.50 (1.41)</td>
<td>6.36 (2.16)</td>
<td>6.89 (2.03)</td>
<td>0.2137</td>
</tr>
<tr>
<td>Pre-eclampsia diagnostic criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max systolic pressure (mm Hg)</td>
<td>139 (25)</td>
<td>172 (18)</td>
<td>159 (20)</td>
<td>131 (15)</td>
<td>155 (30)</td>
<td>1.548e-10</td>
</tr>
<tr>
<td>Max diastolic pressure (mm Hg)</td>
<td>89 (15)</td>
<td>109 (11)</td>
<td>98 (13)</td>
<td>82 (11)</td>
<td>95 (16)</td>
<td>4.18e-11</td>
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<tr>
<td>Max MAP (mm Hg)</td>
<td>105 (18)</td>
<td>129 (11)</td>
<td>117 (14)</td>
<td>97 (10)</td>
<td>114 (20)</td>
<td>3.599e-11</td>
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<tr>
<td>Mode proteinuria level (dipstick)</td>
<td>+1.0 (1.2)</td>
<td>+2.6 (1.3)</td>
<td>+2.1 (0.9)</td>
<td>+0.6 (1.0)</td>
<td>+1.4 (1.4)</td>
<td>3.593e-07</td>
</tr>
<tr>
<td>Blood work</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; trimester hemoglobin (g/L)</td>
<td>138 (6)</td>
<td>134 (6)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.4162</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; trimester hemoglobin (g/L)</td>
<td>123 (10)</td>
<td>124 (12)</td>
<td>123 (12)</td>
<td>117 (9)</td>
<td>118 (9)</td>
<td>0.123</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; trimester hemoglobin (g/L)</td>
<td>119 (10)</td>
<td>125 (13)</td>
<td>120 (11)</td>
<td>112 (7)</td>
<td>120 (12)</td>
<td>5.283e-08</td>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; trimester WBC (x10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>7.9 (3.4)</td>
<td>8.6 (2.4)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.5237</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; trimester WBC (x10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>9.4 (2.0)</td>
<td>10.6 (2.1)</td>
<td>11.3 (2.3)</td>
<td>12.9 (2.7)</td>
<td>11.0 (3.3)</td>
<td>1.846e-05</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; trimester WBC (x10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>11.0 (3.4)</td>
<td>11.4 (2.7)</td>
<td>9.2 (1.5)</td>
<td>12.7 (3.7)</td>
<td>11.5 (3.7)</td>
<td>1.646e-05</td>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; trimester creatinine (mmol/L)</td>
<td>--</td>
<td>52 (5)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; trimester creatinine (mmol/L)</td>
<td>48 (10)</td>
<td>53 (8)</td>
<td>50 (6)</td>
<td>--</td>
<td>--</td>
<td>0.4828</td>
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<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; trimester creatinine (mmol/L)</td>
<td>52 (11)</td>
<td>62 (12)</td>
<td>60 (13)</td>
<td>--</td>
<td>54 (8)</td>
<td>1.755e-09</td>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; trimester platelets (x10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
<td>275 (79)</td>
<td>234 (50)</td>
<td>--</td>
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<td>0.5237</td>
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</table>
### 2nd trimester platelets (x10^9/L)

<table>
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<th>Max (Range)</th>
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<tbody>
<tr>
<td></td>
<td>230 (59)</td>
<td>202 (74)</td>
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<td>270 (52)</td>
<td>264 (51)</td>
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### 3rd trimester platelets (x10^9/L)

<table>
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<th>Max (Range)</th>
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<tbody>
<tr>
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<td>197 (47)</td>
<td>203 (59)</td>
<td>203 (54)</td>
<td>235 (45)</td>
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### 2nd trimester ALT (U/L)

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<tbody>
<tr>
<td></td>
<td>14 (12)</td>
<td>94 (176)</td>
<td>14 (3)</td>
<td>11 (2)</td>
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### 3rd trimester ALT (U/L)

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<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>26 (30)</td>
<td>27 (17)</td>
<td>17 (16)</td>
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<td>26 (36)</td>
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### 2nd trimester AST (U/L)

<table>
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<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>17 (5)</td>
<td>65 (134)</td>
<td>16 (3)</td>
<td>15 (6)</td>
<td>23 (21)</td>
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### 3rd trimester AST (U/L)

<table>
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<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>29 (27)</td>
<td>27 (15)</td>
<td>24 (21)</td>
<td>--</td>
<td>26 (24)</td>
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### 2nd trimester bilirubin (umol/L)

<table>
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<th>Median (IQR)</th>
<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.6 (3.0)</td>
<td>3.7 (2.7)</td>
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<td>0.3064</td>
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### 3rd trimester bilirubin (umol/L)

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<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.4 (2.2)</td>
<td>3.7 (1.7)</td>
<td>3.5 (1.3)</td>
<td>4.3 (2.2)</td>
<td>0.29</td>
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### 2nd trimester uric acid (umol/L)

<table>
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<th>Median (IQR)</th>
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<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>249 (80)</td>
<td>300 (90)</td>
<td>264 (37)</td>
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<td>0.1617</td>
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### 3rd trimester uric acid (umol/L)

<table>
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<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>308 (76)</td>
<td>399 (82)</td>
<td>361 (64)</td>
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<td>0.197</td>
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### PAPPA (MoM)

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<th>Median (IQR)</th>
<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.05 (0.60)</td>
<td>0.90 (0.76)</td>
<td>1.05 (0.96)</td>
<td>1.21 (0.67)</td>
<td>0.88 (0.30)</td>
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### AFP (MoM)

<table>
<thead>
<tr>
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<th>Mean (SD)</th>
<th>Median (IQR)</th>
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<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.17 (0.62)</td>
<td>1.68 (0.66)</td>
<td>1.08 (0.16)</td>
<td>1.06 (0.24)</td>
<td>0.89 (0.23)</td>
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</tbody>
</table>

### hCG (MoM)

<table>
<thead>
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<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.73 (2.25)</td>
<td>2.49 (3.67)</td>
<td>1.27 (0.95)</td>
<td>2.26 (2.14)</td>
<td>1.14 (0.56)</td>
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</table>

### Inhibin A (MoM)

<table>
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<th>Median (IQR)</th>
<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.55 (1.56)</td>
<td>2.16 (1.03)</td>
<td>1.75 (0.36)</td>
<td>--</td>
<td>1.37 (0.64)</td>
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### Unconjugated estriol (MoM)

<table>
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<th>Min (Range)</th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.96 (0.24)</td>
<td>0.89 (0.17)</td>
<td>0.72 (0.19)</td>
<td>0.84 (0.12)</td>
<td>0.77 (0.16)</td>
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### Fetal demographics

<table>
<thead>
<tr>
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<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuchal translucency (mm)</td>
<td>1.58 (0.35)</td>
<td>1.52 (0.41)</td>
<td>1.68 (0.49)</td>
<td>2.52 (1.26)</td>
<td>1.47 (0.24)</td>
</tr>
<tr>
<td>GA at delivery (weeks)</td>
<td>36 (4)</td>
<td>31 (3)</td>
<td>34 (4)</td>
<td>29 (4)</td>
<td>33 (4)</td>
</tr>
<tr>
<td>Newborn weight z-score</td>
<td>-0.13 (1.01)</td>
<td>-1.33 (0.74)</td>
<td>-1.46 (0.89)</td>
<td>0.34 (0.95)</td>
<td>-0.85 (1.15)</td>
</tr>
<tr>
<td>Apgar score at 1 minute (/10)</td>
<td>8.3 (1.2)</td>
<td>7.2 (2.0)</td>
<td>7.4 (2.1)</td>
<td>7.0 (1.7)</td>
<td>7.0 (2.4)</td>
</tr>
<tr>
<td>Apgar score at 5 minutes (/10)</td>
<td>8.9 (0.4)</td>
<td>8.7 (0.8)</td>
<td>8.8 (0.4)</td>
<td>8.1 (2.3)</td>
<td>8.3 (1.2)</td>
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### Placental and umbilical cord data

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min (Range)</th>
<th>Max (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental weight z-score</td>
<td>-0.37 (0.99)</td>
<td>-1.25 (0.76)</td>
<td>-1.31 (1.16)</td>
<td>0.72 (1.37)</td>
<td>-0.98 (0.79)</td>
</tr>
<tr>
<td>Placental surface area (cm²)</td>
<td>1761 (433)</td>
<td>1143 (404)</td>
<td>1382 (653)</td>
<td>1465 (420)</td>
<td>1352 (449)</td>
</tr>
<tr>
<td>Placental thickness (cm)</td>
<td>2.60 (0.72)</td>
<td>2.28 (0.96)</td>
<td>2.05 (0.59)</td>
<td>2.44 (0.50)</td>
<td>2.22 (0.49)</td>
</tr>
<tr>
<td>Placental asymmetry (ratio)</td>
<td>0.13 (0.09)</td>
<td>0.16 (0.11)</td>
<td>0.15 (0.10)</td>
<td>0.15 (0.07)</td>
<td>0.19 (0.18)</td>
</tr>
<tr>
<td>Placental efficiency (ratio)</td>
<td>5.12 (0.99)</td>
<td>4.37 (1.01)</td>
<td>4.77 (0.96)</td>
<td>3.49 (0.97)</td>
<td>4.61 (0.93)</td>
</tr>
<tr>
<td>Cord insertion distance from placental margin (cm)</td>
<td>3.85 (1.49)</td>
<td>2.88 (1.11)</td>
<td>3.21 (1.79)</td>
<td>3.11 (1.45)</td>
<td>3.43 (1.27)</td>
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<tr>
<td>Cord diameter (cm)</td>
<td>1.31 (0.38)</td>
<td>1.12 (0.34)</td>
<td>0.93 (0.31)</td>
<td>1.22 (0.26)</td>
<td>1.21 (0.27)</td>
</tr>
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* Only noted and used if values were available for at least 3 samples in the cluster.

† PI = pulsatility index.
Table S5. Full set of clinical characteristics across the clusters – categorical variables.

<table>
<thead>
<tr>
<th>Clinical Attribute</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
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<tr>
<td>Parental demographics</td>
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<tr>
<td>Nulliparous</td>
<td>50.0 (30/60)</td>
<td>66.1 (37/56)</td>
<td>36.4 (4/11)</td>
<td>50.0 (7/14)</td>
<td>37.5 (6/16)</td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>28.3 (17/60)</td>
<td>26.8 (15/56)</td>
<td>27.3 (3/11)</td>
<td>7.1 (1/14)</td>
<td>25.0 (4/16)</td>
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<tr>
<td>Previous termination</td>
<td>20.0 (12/60)</td>
<td>19.6 (11/56)</td>
<td>27.3 (3/11)</td>
<td>14.3 (2/14)</td>
<td>12.5 (2/16)</td>
</tr>
<tr>
<td>Previous hypertensive pregnancy</td>
<td>30.8 (8/26)</td>
<td>53.3 (8/15)</td>
<td>28.6 (2/7)</td>
<td>20.0 (1/5)</td>
<td>50.0 (3/5)</td>
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<td>Maternal Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>66.7 (38/57)</td>
<td>44.6 (25/56)</td>
<td>27.3 (3/11)</td>
<td>64.3 (9/14)</td>
<td>66.7 (10/15)</td>
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<tr>
<td>Black</td>
<td>8.8 (5/57)</td>
<td>23.2 (13/56)</td>
<td>36.4 (4/11)</td>
<td>14.3 (2/14)</td>
<td>0 (0/15)</td>
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<tr>
<td>Asian</td>
<td>17.5 (10/57)</td>
<td>21.4 (12/56)</td>
<td>27.3 (3/11)</td>
<td>7.1 (1/14)</td>
<td>20.0 (3/15)</td>
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<tr>
<td>East Indian</td>
<td>5.3 (3/57)</td>
<td>7.1 (4/56)</td>
<td>9.1 (1/11)</td>
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<td>0 (0/15)</td>
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<tr>
<td>Paternal Ethnicity</td>
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<td></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>87.5 (21/24)</td>
<td>36.9 (7/19)</td>
<td>40.0 (2/5)</td>
<td>71.4 (5/7)</td>
<td>100 (5/5)</td>
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<tr>
<td>Black</td>
<td>4.2 (1/24)</td>
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<td>14.3 (1/7)</td>
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<td>0 (0/5)</td>
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<td>Maternal blood type</td>
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</tr>
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<td>A</td>
<td>21.7 (13/60)</td>
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<td>28.6 (4/14)</td>
<td>18.8 (3/16)</td>
</tr>
<tr>
<td>O</td>
<td>48.3 (29/60)</td>
<td>30.9 (17/55)</td>
<td>18.2 (2/11)</td>
<td>42.9 (6/14)</td>
<td>56.3 (9/16)</td>
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<td>AB</td>
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<td>Rh positive</td>
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<td>98.1 (53/54)</td>
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<td>87.5 (14/16)</td>
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<tr>
<td>BMI &gt; 25 kg/m²</td>
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<td>66.7 (30/45)</td>
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<td>40.0 (6/15)</td>
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<td>Asthma</td>
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<td>17.4 (8/46)</td>
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<td>16.7 (2/12)</td>
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<td>History of STDs</td>
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<td>Renal problems</td>
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<td>Anxiety/Depression</td>
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<td>Chronic hypertension</td>
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<td>Ultrasound data</td>
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<td>Placenta position on ultrasound</td>
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<td>Anterior</td>
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<td>48.3 (14/29)</td>
<td>66.7 (4/6)</td>
<td>42.9 (3/7)</td>
<td>33.3 (2/6)</td>
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<td>Posterior</td>
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<td>55.2 (16/29)</td>
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<td>50.0 (3/6)</td>
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<td>Amniotic fluid deficiency</td>
<td>16.7 (2/12)</td>
<td>29.2 (7/24)</td>
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<td>62.5 (5/8)</td>
<td>33.3 (1/3)</td>
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### Medications

<table>
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<tr>
<th>Medication</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1 vaccine in pregnancy</td>
<td>20.0 (12/60)</td>
<td>10.1 (6/56)</td>
<td>9.1 (1/11)</td>
<td>14.3 (2/14)</td>
<td>18.9 (3/16)</td>
<td>0.6737</td>
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<td>Prenatal vitamins</td>
<td>60.0 (36/60)</td>
<td>51.8 (29/56)</td>
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<td>50.0 (7/14)</td>
<td>43.8 (7/16)</td>
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<td>Folic acid</td>
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<td>0 (0/16)</td>
<td>0.6138</td>
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<td>Acetaminophen treatment</td>
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<td>18.8 (3/16)</td>
<td>0.6737</td>
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<td></td>
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<tr>
<td>Aspirin treatment</td>
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<td>Morphine treatment</td>
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<td>Colace treatment</td>
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<td>17.9 (10/56)</td>
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<td>Anti-nausea treatment</td>
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<td>26.8 (15/56)</td>
<td>9.1 (1/11)</td>
<td>50.0 (7/14)</td>
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<td>0.01908</td>
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<td>Acid reflux treatment</td>
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<td>16.1 (9/56)</td>
<td>9.1 (1/11)</td>
<td>14.3 (2/14)</td>
<td>0 (0/16)</td>
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<tr>
<td>Anti-anxiety treatment</td>
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<td>10.7 (6/56)</td>
<td>0 (0/11)</td>
<td>14.3 (2/14)</td>
<td>0 (0/16)</td>
<td>0.2289</td>
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<tr>
<td>Antibiotic treatment</td>
<td>43.3 (26/60)</td>
<td>42.9 (24/56)</td>
<td>36.4 (4/11)</td>
<td>71.4 (10/14)</td>
<td>56.3 (9/16)</td>
<td>0.2838</td>
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<tr>
<td>Anti-hypertensive treatment</td>
<td>28.3 (17/60)</td>
<td>83.9 (47/56)</td>
<td>63.6 (7/11)</td>
<td>21.4 (3/14)</td>
<td>62.5 (10/16)</td>
<td>1.137e-09</td>
</tr>
<tr>
<td>Steroid administration</td>
<td>18.3 (11/60)</td>
<td>71.4 (40/56)</td>
<td>36.4 (4/11)</td>
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<td>43.8 (7/16)</td>
<td>7.359e-08</td>
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### Diagnoses

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<th>Diagnosis</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia diagnosis</td>
<td>23.3 (14/60)</td>
<td>89.3 (50/56)</td>
<td>72.7 (8/11)</td>
<td>7.1 (1/14)</td>
<td>43.8 (7/16)</td>
<td>2.635e-15</td>
</tr>
<tr>
<td>HELLP diagnosis</td>
<td>1.7 (1/60)</td>
<td>32.1 (18/56)</td>
<td>9.1 (1/11)</td>
<td>0 (0/14)</td>
<td>12.5 (2/16)</td>
<td>2.545e-05</td>
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<tr>
<td>IUGR diagnosis</td>
<td>8.3 (5/60)</td>
<td>41.1 (23/56)</td>
<td>63.6 (7/11)</td>
<td>0 (0/14)</td>
<td>31.3 (5/16)</td>
<td>1.505e-06</td>
</tr>
<tr>
<td>Chorioamnionitis diagnosis</td>
<td>6.7 (4/60)</td>
<td>0 (0/56)</td>
<td>0 (0/11)</td>
<td>71.4 (10/14)</td>
<td>12.5 (2/16)</td>
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### Labor and Delivery

<table>
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<tr>
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<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous labor</td>
<td>30.0 (18/60)</td>
<td>3.6 (2/56)</td>
<td>0 (0/11)</td>
<td>92.9 (13/14)</td>
<td>6.7 (1/15)</td>
</tr>
<tr>
<td>Attempted vaginal delivery</td>
<td>50.0 (30/60)</td>
<td>30.4 (17/56)</td>
<td>9.1 (1/11)</td>
<td>100 (14/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>38.3 (23/60)</td>
<td>12.5 (7/56)</td>
<td>9.1 (1/11)</td>
<td>64.3 (9/14)</td>
<td>18.8 (3/16)</td>
</tr>
<tr>
<td>Delivery &lt; 34 weeks</td>
<td>28.3 (17/60)</td>
<td>78.6 (44/56)</td>
<td>36.4 (4/11)</td>
<td>85.7 (12/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>Delivery &lt; 37 weeks</td>
<td>43.3 (26/60)</td>
<td>91.1 (51/56)</td>
<td>72.7 (8/11)</td>
<td>92.9 (13/14)</td>
<td>75.0 (12/16)</td>
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### Fetal demographics

<table>
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<tr>
<th>Event</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male fetus</td>
<td>51.7 (31/60)</td>
<td>57.1 (32/56)</td>
<td>45.5 (5/11)</td>
<td>57.1 (8/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>AGA (10-90th percentile)</td>
<td>85.0 (51/60)</td>
<td>44.6 (25/56)</td>
<td>36.4 (4/11)</td>
<td>78.6 (11/14)</td>
<td>50.0 (8/16)</td>
</tr>
<tr>
<td>SGA (&lt;10th percentile)</td>
<td>51.7 (31/60)</td>
<td>57.1 (32/56)</td>
<td>45.5 (5/11)</td>
<td>57.1 (8/14)</td>
<td>43.8 (7/16)</td>
</tr>
<tr>
<td>NICU transfer</td>
<td>18.3 (11/60)</td>
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<td>36.4 (4/11)</td>
<td>42.9 (6/14)</td>
<td>37.5 (6/16)</td>
</tr>
</tbody>
</table>

* All available data was utilized, however, information was missing for some samples for some characteristics. Complete data is indicated by N=60 for cluster 1, N=56 for cluster 2, N=11 for cluster 3, N=14 for cluster 4, and N=16 for cluster 5.
Table S6. Full set of clinical characteristics across the PE subclasses – continuous variables.

<table>
<thead>
<tr>
<th>Clinical Attribute</th>
<th>Mean (SD)</th>
<th>P-value</th>
</tr>
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<tr>
<td><strong>Parental demographics</strong></td>
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</tr>
<tr>
<td>Maternal age (years)</td>
<td>30.5 (4.5)</td>
<td>0.08579</td>
</tr>
<tr>
<td>Paternal age (years)</td>
<td>34.3 (3.3)</td>
<td>0.3038</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>26.7 (9.4)</td>
<td>0.375</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td>163 (5)</td>
<td>0.2235</td>
</tr>
<tr>
<td><strong>Uteroplacental blood flow/Ultrasound data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean uterine artery PI †</td>
<td>0.97 (0.43)</td>
<td>0.01638</td>
</tr>
<tr>
<td>Max uterine artery PI †</td>
<td>1.05 (0.39)</td>
<td>0.04319</td>
</tr>
<tr>
<td>Mean umbilical artery PI †</td>
<td>1.11 (0.22)</td>
<td>0.03817</td>
</tr>
<tr>
<td>Max umbilical artery PI †</td>
<td>1.24 (0.28)</td>
<td>0.07767</td>
</tr>
<tr>
<td>Mean middle cerebral artery PI †</td>
<td>1.87 (0.39)</td>
<td>0.1016</td>
</tr>
<tr>
<td>Min middle cerebral artery PI †</td>
<td>1.73 (0.49)</td>
<td>0.1858</td>
</tr>
<tr>
<td>Mean MCA peak systolic velocity (cm/sec)</td>
<td>50.0 (13.4)</td>
<td>0.7637</td>
</tr>
<tr>
<td>Max MCA peak systolic velocity (cm/sec)</td>
<td>55.2 (18.8)</td>
<td>0.9454</td>
</tr>
<tr>
<td>Mean biophysical profile score (/10)</td>
<td>7.7 (0.6)</td>
<td>0.1232</td>
</tr>
<tr>
<td>Min biophysical profile score (/10)</td>
<td>7.6 (0.8)</td>
<td>0.1022</td>
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<tr>
<td><strong>Preeclampsia diagnostic criteria</strong></td>
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</tr>
<tr>
<td>Max systolic pressure (mm Hg)</td>
<td>167 (17)</td>
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</tr>
<tr>
<td>Max diastolic pressure (mm Hg)</td>
<td>103 (8)</td>
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</tr>
<tr>
<td>Max MAP (mm Hg)</td>
<td>124 (9)</td>
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<td>Mode proteinuria level (dipstick)</td>
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<tr>
<td><strong>Blood work</strong></td>
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<tr>
<td>1st trimester hemoglobin (g/L)</td>
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<tr>
<td>2nd trimester hemoglobin (g/L)</td>
<td>124 (10)</td>
<td>0.3128</td>
</tr>
<tr>
<td>3rd trimester hemoglobin (g/L)</td>
<td>119 (10)</td>
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</tr>
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<td>1st trimester WBC (x10³/mm³)</td>
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<td>2nd trimester WBC (x10³/mm³)</td>
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<td>1st trimester creatinine (mmol/L)</td>
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<td>2nd trimester creatinine (mmol/L)</td>
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<td>3rd trimester creatinine (mmol/L)</td>
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<td>2nd trimester platelets (x10⁹/L)</td>
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<tr>
<td>3rd trimester platelets (x10⁹/L)</td>
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<tr>
<td></td>
<td>2nd trimester platelets (x10^9/L)</td>
<td>3rd trimester platelets (x10^9/L)</td>
</tr>
<tr>
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<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
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<td>201 (45)</td>
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<tr>
<td>Nuchal translucency (mm)</td>
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<tr>
<td>GA at delivery (weeks)</td>
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<td>Newborn weight z-score</td>
<td>7.9 (1.2)</td>
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<td>8.8 (0.6)</td>
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<td>Apgar score at 5 minutes (/10)</td>
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* Only noted and used if values were available for at least 3 samples in the subclass.

† PI = pulsatility index.
Table S7. Full set of clinical characteristics across the PE subclasses – categorical variables.

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<thead>
<tr>
<th>Clinical Attribute</th>
<th>Cluster 1 PE</th>
<th>Cluster 2 PE</th>
<th>Cluster 3 PE</th>
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<td>Nulliparous</td>
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<td>37.5 (3/8)</td>
<td>57.1 (4/7)</td>
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<td>14.3 (1/7)</td>
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<tr>
<td>Previous termination</td>
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<tr>
<td>Previous hypertensive pregnancy</td>
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<td>37.5 (3/8)</td>
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<td>37.5 (3/8)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>Asian</td>
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<td>20.0 (10/50)</td>
<td>12.5 (1/8)</td>
<td>0 (0/6)</td>
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<tr>
<td>East Indian</td>
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<td>6.0 (3/50)</td>
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<td>0 (0/6)</td>
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<td>Paternal Ethnicity</td>
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<tr>
<td>Caucasian</td>
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<td>50.0 (2/4)</td>
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<tr>
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<td>25.0 (1/4)</td>
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</tr>
<tr>
<td>Asian</td>
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<td>25.0 (1/4)</td>
<td>0 (0/4)</td>
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<tr>
<td>East Indian</td>
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<td>0 (0/4)</td>
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<tr>
<td>Maternal blood type</td>
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<td>A</td>
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<td>62.5 (5/8)</td>
<td>14.3 (1/7)</td>
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<td>B</td>
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<td>12.5 (1/8)</td>
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<td>O</td>
<td>78.6 (11/14)</td>
<td>30.6 (15.49)</td>
<td>25.0 (2/8)</td>
<td>71.4 (5/7)</td>
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<td>Rh positive</td>
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<td>87.5 (7/8)</td>
<td>71.4 (5/7)</td>
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<td>BMI &gt; 25 kg/m²</td>
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<td>70.7 (29/41)</td>
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<td>50.0 (3/6)</td>
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<td>Asthma</td>
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<td>History of STDs</td>
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<td>0 (0/4)</td>
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<td>25.0 (1/4)</td>
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<td>Anxiety/Depression</td>
<td>15.4 (2/13)</td>
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<td>Chronic hypertension</td>
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<td>14.3 (1/7)</td>
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<td>Anterior</td>
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<td>Posterior</td>
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<td>57.7 (15/26)</td>
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<td>Amniotic fluid deficiency</td>
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<td>29.2 (7/24)</td>
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<td>0 (0/2)</td>
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<td>Medications</td>
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P-value
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<th>Characteristics</th>
<th>Cluster 1 (PE)</th>
<th>Cluster 2 (PE)</th>
<th>Cluster 3 (PE)</th>
<th>Cluster 5 (PE)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1 vaccine in pregnancy</td>
<td>28.6 (4/14)</td>
<td>12.0 (6/50)</td>
<td>12.5 (1/8)</td>
<td>28.6 (2/7)</td>
<td>0.2876</td>
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<td>Prenatal vitamins</td>
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<td>42.9 (3/7)</td>
<td>0.7231</td>
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<tr>
<td>Folic acid</td>
<td>7.1 (1/14)</td>
<td>12.0 (6/50)</td>
<td>0 (0/8)</td>
<td>0 (0/7)</td>
<td>0.9181</td>
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<tr>
<td>Acetaminophen treatment</td>
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<td>28.6 (2/7)</td>
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<td>Aspirin treatment</td>
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<td>Morphine treatment</td>
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<td>Colace treatment</td>
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<td>0 (0/8)</td>
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<td>Anti-nausea treatment</td>
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<td>18.0 (9/50)</td>
<td>12.5 (1/8)</td>
<td>0 (0/7)</td>
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</tr>
<tr>
<td>Anti-anxiety treatment</td>
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<td>12.0 (6/50)</td>
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<td>0 (0/7)</td>
<td>0.9181</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>42.9 (6/14)</td>
<td>46.0 (23/50)</td>
<td>25.0 (2/8)</td>
<td>71.4 (5/7)</td>
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<td>Anti-hypertensive treatment</td>
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<td>86.0 (43/50)</td>
<td>62.5 (5/8)</td>
<td>85.7 (6/7)</td>
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<td>Steroid administration</td>
<td>21.4 (3/14)</td>
<td>72.0 (36/50)</td>
<td>25.0 (2/8)</td>
<td>42.9 (3/7)</td>
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**Diagnoses**

<table>
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<tr>
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<th>Cluster 1 (PE)</th>
<th>Cluster 2 (PE)</th>
<th>Cluster 3 (PE)</th>
<th>Cluster 5 (PE)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia diagnosis</td>
<td>100 (14/14)</td>
<td>100 (50/50)</td>
<td>100 (8/8)</td>
<td>100 (7/7)</td>
<td>--</td>
</tr>
<tr>
<td>HELLP diagnosis</td>
<td>7.1 (1/14)</td>
<td>36.0 (18/50)</td>
<td>12.5 (1/8)</td>
<td>28.6 (2/7)</td>
<td>0.1232</td>
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<tr>
<td>IUGR diagnosis</td>
<td>0 (0/14)</td>
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<td>62.5 (5/8)</td>
<td>28.6 (2/7)</td>
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<tr>
<td>Chorioamnionitis diagnosis</td>
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**Labor and Delivery**

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<th>Event</th>
<th>Cluster 1 (PE)</th>
<th>Cluster 2 (PE)</th>
<th>Cluster 3 (PE)</th>
<th>Cluster 5 (PE)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous labor</td>
<td>0 (0/6)</td>
<td>6.3 (1/16)</td>
<td>0 (0/1)</td>
<td>0 (0/4)</td>
<td>1</td>
</tr>
<tr>
<td>Attempted vaginal delivery</td>
<td>42.9 (6/14)</td>
<td>32.0 (16/50)</td>
<td>12.5 (1/8)</td>
<td>57.1 (4/7)</td>
<td>0.2914</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>42.9 (6/14)</td>
<td>12.0 (6/50)</td>
<td>12.5 (1/8)</td>
<td>28.6 (2/7)</td>
<td>0.04917</td>
</tr>
<tr>
<td>Delivery &lt; 34 weeks</td>
<td>28.6 (4/14)</td>
<td>80.0 (40/50)</td>
<td>25.0 (2/8)</td>
<td>42.9 (3/7)</td>
<td>0.0001075</td>
</tr>
<tr>
<td>Delivery &lt; 37 weeks</td>
<td>50.0 (7/14)</td>
<td>94.0 (47/50)</td>
<td>75 (6/8)</td>
<td>100 (7/7)</td>
<td>0.0007283</td>
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**Fetal demographics**

<table>
<thead>
<tr>
<th>Event</th>
<th>Cluster 1 (PE)</th>
<th>Cluster 2 (PE)</th>
<th>Cluster 3 (PE)</th>
<th>Cluster 5 (PE)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male fetus</td>
<td>50.0 (7/14)</td>
<td>56.0 (28/50)</td>
<td>50.0 (4/8)</td>
<td>28.6 (2/7)</td>
<td>0.634</td>
</tr>
<tr>
<td>AGA (10-90th percentile)</td>
<td>85.7 (12/14)</td>
<td>46.0 (23/50)</td>
<td>25.0 (2/8)</td>
<td>42.9 (3/7)</td>
<td>0.01906</td>
</tr>
<tr>
<td>SGA (&lt;10th percentile)</td>
<td>14.3 (2/14)</td>
<td>54.0 (27/50)</td>
<td>75.0 (6/8)</td>
<td>57.1 (4/7)</td>
<td>0.01906</td>
</tr>
<tr>
<td>NICU transfer</td>
<td>21.4 (3/14)</td>
<td>54.0 (27/50)</td>
<td>25.0 (2/8)</td>
<td>28.6 (2/7)</td>
<td>0.08775</td>
</tr>
</tbody>
</table>

* All available data was utilized, however, information was missing for some samples for some characteristics. Complete data is indicated by N=14 for cluster 1 PE, N=50 for cluster 2 PE, N=8 for cluster 3 PE, and N=7 for cluster 5 PE.
Table S8. Intra-cluster maternal differences between preeclamptics and non-preeclamptics. Statistically significant findings (p < 0.05) are shaded in grey.

Cluster 1:

<table>
<thead>
<tr>
<th>Clinical Attribute</th>
<th>Non-PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>33 (5)</td>
<td>31 (4)</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
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<table>
<thead>
<tr>
<th>Clinical Attribute</th>
<th>Percentage of Phenotype (n/N)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous (prior to this pregnancy)</td>
<td>43.4 (20/46)</td>
<td>71.4 (10/14)</td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>32.6 (15/46)</td>
<td>14.3 (2/14)</td>
</tr>
<tr>
<td>Previous termination</td>
<td>15.2 (7/46)</td>
<td>35.7 (5/14)</td>
</tr>
<tr>
<td>Previous hypertensive pregnancy</td>
<td>18.2 (4/22)</td>
<td>100 (4/4)</td>
</tr>
<tr>
<td>Maternal Ethnicity</td>
<td></td>
<td>0.293</td>
</tr>
<tr>
<td>Caucasian</td>
<td>61.3 (27/44)</td>
<td>84.6 (11/13)</td>
</tr>
<tr>
<td>Black</td>
<td>9.1 (4/44)</td>
<td>7.7 (1/13)</td>
</tr>
<tr>
<td>Asian</td>
<td>22.7 (10/44)</td>
<td>0 (0/13)</td>
</tr>
<tr>
<td>East Indian</td>
<td>4.5 (2/44)</td>
<td>7.7 (1/13)</td>
</tr>
<tr>
<td>Maternal blood type</td>
<td></td>
<td>0.09058</td>
</tr>
<tr>
<td>A</td>
<td>23.9 (11/46)</td>
<td>14.3 (2/14)</td>
</tr>
<tr>
<td>B</td>
<td>32.6 (15/46)</td>
<td>7.1 (1/14)</td>
</tr>
<tr>
<td>O</td>
<td>39.1 (18/46)</td>
<td>78.6 (11/14)</td>
</tr>
<tr>
<td>AB</td>
<td>4.3 (2/46)</td>
<td>0 (0/14)</td>
</tr>
<tr>
<td>Rh positive</td>
<td>87.0 (40/46)</td>
<td>92.8 (13/14)</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>35.6 (16/45)</td>
<td>42.8 (6/14)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>26.1 (12/46)</td>
<td>14.3 (2/14)</td>
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* Information was not available for all patients for all attributes. Full data is N=46 for non-preeclamptics and N=14 for preeclamptics.
Cluster 2:

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<th>P-value</th>
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<tr>
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<td>33 (6)</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 (3.8)</td>
<td>26.8 (4.2)</td>
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<table>
<thead>
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<th>Percentage of Phenotype (n/N) *</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous (prior to this pregnancy)</td>
<td>83.3 (5/6)</td>
<td>64.0 (32/50)</td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>16.6 (1/6)</td>
<td>28.0 (14/50)</td>
</tr>
<tr>
<td>Previous termination</td>
<td>16.6 (1/6)</td>
<td>20.0 (10/50)</td>
</tr>
<tr>
<td>Previous hypertensive pregnancy</td>
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<td>53.3 (8/15)</td>
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<tr>
<td>Maternal Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>40.0 (2/5)</td>
<td>46.0 (23/50)</td>
</tr>
<tr>
<td>Black</td>
<td>20.0 (1/5)</td>
<td>24.0 (12/50)</td>
</tr>
<tr>
<td>Asian</td>
<td>40.0 (2/5)</td>
<td>20.0 (10/50)</td>
</tr>
<tr>
<td>East Indian</td>
<td>20.0 (1/5)</td>
<td>6.0 (3/50)</td>
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<td>33.3 (2/6)</td>
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<td>33.3 (2/6)</td>
<td>20.4 (10/49)</td>
</tr>
<tr>
<td>O</td>
<td>33.3 (2/6)</td>
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</tr>
<tr>
<td>AB</td>
<td>0 (0/6)</td>
<td>6.1 (3/49)</td>
</tr>
<tr>
<td>Rh positive</td>
<td>100 (6/6)</td>
<td>97.9 (47/48)</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>25.0 (1/4)</td>
<td>70.7 (29/41)</td>
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<tr>
<td>Chronic hypertension</td>
<td>83.3 (5/6)</td>
<td>24.0 (12/50)</td>
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* Information was not available for all patients for all attributes. Full data is N=6 for non-preeclamptics and N=50 for preeclamptics.
Cluster 3:

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<table>
<thead>
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<th>P-value</th>
</tr>
</thead>
<tbody>
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<td>Previous termination</td>
<td>33.3 (1/3) 25.0 (2/8)</td>
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<td>Previous hypertensive pregnancy</td>
<td>0 (0/2) 40.0 (2/5)</td>
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<td>Maternal Ethnicity</td>
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<tr>
<td>Black</td>
<td>33.3 (1/3) 37.5 (3/8)</td>
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</tr>
<tr>
<td>Asian</td>
<td>66.7 (2/3) 12.5 (1/8)</td>
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</tr>
<tr>
<td>East Indian</td>
<td>0 (0/3) 12.5 (1/8)</td>
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<table>
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<th>Percentage of Phenotype (n/N)*</th>
<th>P-value</th>
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<tbody>
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<td>A</td>
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</tr>
<tr>
<td>B</td>
<td>100 (3/3) 12.5 (1/8)</td>
<td>--</td>
</tr>
<tr>
<td>O</td>
<td>0 (0/3) 25.0 (2/8)</td>
<td>--</td>
</tr>
<tr>
<td>AB</td>
<td>0 (0/3) 0 (0/8)</td>
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<tr>
<td>Rh positive</td>
<td>100 (3/3) 87.5 (7/8)</td>
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<td>BMI &gt; 25 kg/m^2</td>
<td>50.0 (1/2) 42.9 (3/7)</td>
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<tr>
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<td>66.7 (2/3) 25.0 (2/8)</td>
<td>0.4909</td>
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* Information was not available for all patients for all attributes. Full data is N=3 for non-preeclamptics and N=8 for preeclamptics.
Cluster 5:

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<th>Non-PE Mean (SD)</th>
<th>PE Mean (SD)</th>
<th>P-value</th>
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<table>
<thead>
<tr>
<th>Clinical Attribute</th>
<th>Percentage of Phenotype (n/N)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous (prior to this pregnancy)</td>
<td>22.2 (2/9)</td>
<td>57.1 (4/7)</td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>33.3 (3/9)</td>
<td>14.3 (1/7)</td>
</tr>
<tr>
<td>Previous termination</td>
<td>0 (0/9)</td>
<td>28.6 (2/7)</td>
</tr>
<tr>
<td>Previous hypertensive pregnancy</td>
<td>50.0 (2/4)</td>
<td>50.0 (1/2)</td>
</tr>
<tr>
<td>Maternal Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>44.4 (4/9)</td>
<td>100 (6/6)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0/9)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>Asian</td>
<td>33.3 (3/9)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>East Indian</td>
<td>0 (0/9)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>Maternal blood type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>22.2 (2/9)</td>
<td>14.3 (1/7)</td>
</tr>
<tr>
<td>B</td>
<td>22.2 (2/9)</td>
<td>0 (0/7)</td>
</tr>
<tr>
<td>O</td>
<td>44.4 (4/9)</td>
<td>71.4 (5/7)</td>
</tr>
<tr>
<td>AB</td>
<td>11.1 (1/9)</td>
<td>14.3 (1/7)</td>
</tr>
<tr>
<td>Rh positive</td>
<td>100 (9/9)</td>
<td>71.4 (2/7)</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>33.3 (3/9)</td>
<td>50.0 (3/6)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>55.6 (5/9)</td>
<td>14.3 (1/7)</td>
</tr>
</tbody>
</table>

* Information was not available for all patients for all attributes. Full data is N=9 for non-preeclamptics and N=7 for preeclamptics.
**Table S10. Comparison of PE-IUGR samples in clusters 2 and 3 by histology – Full Table.** Statistically significant (p < 0.05) features are shaded in grey.

<table>
<thead>
<tr>
<th>Histological Attribute</th>
<th>Percentage of Group (n/N)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral cord insertion</td>
<td>10.5 (2/19)</td>
<td>0.5212</td>
</tr>
<tr>
<td>Velamentous cord insertion</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Extrachorialis</td>
<td>5.3 (1/19)</td>
<td>0.3804</td>
</tr>
<tr>
<td>2 vessel cord</td>
<td>5.3 (1/19)</td>
<td>0.3804</td>
</tr>
<tr>
<td>Excess cord coiling for GA</td>
<td>5.3 (1/19)</td>
<td>1</td>
</tr>
<tr>
<td>True knots</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Accessory lobes</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Comprehensive retroplacental hematoma</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Maternal surface fibrin</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Intervillous fibrin</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Lesion resemble infarcts</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Intervillous thrombi resemble infarcts</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Distal villous hypoplasia</td>
<td>84.2 (16/19)</td>
<td>0.07849</td>
</tr>
<tr>
<td>Placental infarction</td>
<td>68.4 (13/19)</td>
<td>0.01087</td>
</tr>
<tr>
<td>Advanced villous maturity</td>
<td>94.7 (18/19)</td>
<td>0.09881</td>
</tr>
<tr>
<td>Syncytilial knots</td>
<td>89.5 (17/19)</td>
<td>0.006494</td>
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<tr>
<td>Focal perivillous fibrin deposition</td>
<td>5.3 (1/19)</td>
<td>0.09881</td>
</tr>
<tr>
<td>Insufficient vessel remodeling</td>
<td>0 (0/5)</td>
<td>--</td>
</tr>
<tr>
<td>Fibrinoid change</td>
<td>0 (0/5)</td>
<td>--</td>
</tr>
<tr>
<td>Chorangiosis</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Choriangiomas</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Local choriangiomatosis</td>
<td>5.3 (1/19)</td>
<td>1</td>
</tr>
<tr>
<td>Multifocal choriangiomatosis</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Villous immaturity and/or dysmaturity</td>
<td>15.8 (3/19)</td>
<td>0.07849</td>
</tr>
<tr>
<td>Avascular fibrotic villi</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Fetal vascular thrombotic lesions and/or hemorrhage endovascularure</td>
<td>15.8 (3/19)</td>
<td>1</td>
</tr>
<tr>
<td>Subintimal fibrin cushions</td>
<td>5.6 (1/18)</td>
<td>1</td>
</tr>
<tr>
<td>Chorionic hemosiderosis</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Retroplacental adhesion blood clots</td>
<td>10.5 (2/19)</td>
<td>0.5212</td>
</tr>
<tr>
<td>Laminar necrosis of decidua capsularis</td>
<td>0 (0/5)</td>
<td>--</td>
</tr>
<tr>
<td>Massive perivillous fibrin deposition</td>
<td>0 (0/19)</td>
<td>0.004941</td>
</tr>
<tr>
<td>Intervillous thrombi</td>
<td>21.1 (4/19)</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic villitis</td>
<td>5.3 (1/19)</td>
<td>0.3804</td>
</tr>
<tr>
<td>Infectious villitis</td>
<td>0 (0/19)</td>
<td>--</td>
</tr>
<tr>
<td>Chronic deciduitis</td>
<td>10.5 (2/19)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic plasma cell deciduitis</td>
<td>0 (0/19)</td>
<td>0.2083</td>
</tr>
<tr>
<td>Intervillous histocytosis</td>
<td>5.3 (1/19)</td>
<td>0.3804</td>
</tr>
</tbody>
</table>

*Some histological features could not be assessed in all samples. Full data is N=19 for cluster 2 PE-IUGR and N=5 for cluster 3 PE-IUGR.
Figure S1. Principal component analysis (PCA) plots for the visualization of important clinical attributes in the BioBank samples only. Cluster 1 is circled in black; cluster 2 is circled in red; cluster 3 is circled in green; cluster 4 is circled in blue; and cluster 5 is circled in cyan. (A) Placentas in clusters 4 and 2 were the youngest, while most samples in cluster 1 were delivered at or close to term (preterm: < 34 weeks). (B) Two main groups of samples with co-occurring IUGR were identified in clusters 2 and 3, in addition to a few samples in clusters 1 and 5. (C) Most placentas associated with hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome were found dispersed throughout cluster 2. (D) 10 out of 12 preterm control placentas in cluster 4 reported signs of infection (predominately chorioamnionitis). This was in contrast to only 3 (out of 11) preterm controls belonging to cluster 1 that showed signs of infection, and these were found to plot on the outskirts of cluster 1, bordering cluster 4.
Figure S2. Histological comparison of cluster 2 and cluster 3 PE-IUGR placental tissue. (A) Representative micrographs of placental tissue from cluster 2 PE-IUGR members. Placental villi exhibit the distal villous hypoplasia growth pattern as shown by sparsely distributed and small distal villi with thin intermediate villi (indicated with stars). Increased syncytial knots (indicated with arrows) are also seen and are consistent with pathological features of maternal malperfusion. (B) Representative micrographs of placental tissue from cluster 3 PE-IUGR members. A massive perivillus fibrin deposition pattern is seen as expansive fibrin within in the intervillous space (white areas) occupying significant proportion of the overall intervillous space (indicated by arrows). This pattern was detected in three out of five cluster 3 PE-IUGR samples.
Figure S3. Correlations between log2 expression microarray data and log2 fold change over reference quantitative polymerase chain reaction (qPCR) data for the 14 genes and 33 samples assessed by qPCR. Cluster 1 samples – Black; Cluster 2 samples – Red; Cluster 3 samples – Green; Cluster 4 samples – Blue; Cluster 5 samples – Cyan. Correlations and p-values were calculated by Pearson's product-moment correlation in R 3.1.3.
Figure S4. Cluster 5 quantitative polymerase chain reaction (qPCR) results. The cluster 5 samples that were misclassified as cluster 1 (dark cyan) were in line with cluster 1 (black) on the principal component 1 (PC1) axis and were diagnosed as a preterm control and a term PE sample with an averaged sized infant. The cluster 5 samples classified as cluster 2 (purple) were in line with cluster 2 (red) on the PC1 axis and were diagnosed as a preterm PE sample and a PE sample associated with a severely growth restricted infant. The cluster 5 sample misclassified as cluster 4 (sky blue) demonstrated a more positive PC2 value and therefore plotted closer to cluster 4 (blue). Only the 33 BioBank samples assessed by qPCR are colored.