Table S1  Demographic characteristics according to responsiveness to methyldopa and total antihypertensive therapy

| Parameters                  | Methyldopa Responsiveness | Antihypertensive Responsiveness |
|-----------------------------|---------------------------|---------------------------------|
|                             | Responsive (n = 56) | Nonresponsive (n = 125) | p-value | Responsive (n = 102) | Nonresponsive (n = 79) | p-value |
| Age (years)                 | 27 ± 1                  | 26 ± 1                         | 0.54    | 27 ± 1              | 27 ± 1                   | 1.0     |
| Ethnicity (% White)         | 39 (70)                 | 87 (70)                        | 0.63    | 72 (71)             | 55 (70)                  | 0.88    |
| Current Smoking (%)         | 6 (10)                  | 11 (9)                         | 0.55    | 12 (12)             | 4 (5)                     | 0.11    |
| BMI (Kg/m²)                 | 29 ± 1                  | 26 ± 1                         | 0.07    | 29 ± 1              | 27 ± 1                   | 0.16    |
| SBP (mmHg)                  | 130 ± 1                 | 148 ± 1                        | <0.0001 | 135 ± 2             | 151 ± 2                  | <0.0001 |
| DPP (mmHg)                  | 81 ± 1                  | 92 ± 1                         | <0.0001 | 85 ± 1              | 94 ± 1                    | <0.0001 |
| Fasting Glucose (mg/dL)     | 80 ± 2                  | 79 ± 2                         | 0.76    | 78 ± 2              | 81 ± 3                    | 0.39    |
| 24-h-Pr (mg/24h)            | 634 ± 127               | 1559 ± 191                    | <0.0001 | 1087 ± 199          | 1591 ± 213               | 0.09    |
| Primiparity (%)             | 20 (36)                 | 60 (48)                        | 0.57    | 43 (42)             | 37 (47)                   | 0.53    |
| GAD (weeks)                 | 39 ± 1                  | 35 ± 1                         | 0.01    | 38 ± 1              | 34 ± 1                   | <0.0001 |
| Newborn weight (g)          | 3256 ± 81               | 2245 ± 74                     | <0.0001 | 2921 ± 75           | 1989 ± 91                 | <0.0001 |
| GAS (weeks)                 | 35 ± 1                  | 34 ± 1                         | 0.54    | 35 ± 1              | 33 ± 1                   | 0.16    |

GH, gestational hypertension; PE, preeclampsia; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24-h-Pr, 24-h proteinuria; GAD, gestational age at delivery; GAS, gestational age at sampling. Values are the mean ± S.E.M.

Table S2  Robust MDR interaction model among the NFE2L2, HMOX1 and NOS3 polymorphisms when PE patients were compared with HP subjects

| Interaction Models                  | Training score | Testing score | CVC     | p-value |
|-------------------------------------|----------------|---------------|---------|---------|
| NOS3 rs2070744                      | 0.5652         | 0.5469        | 9/10    | –       |
| NFE2L2 rs35652124; HMOX1 rs2071746  | 0.5912         | 0.5620        | 9/10    | 0.3620  |
| NFE2L2 rs35652124; HMOX1 rs2071746; NOS3 rs207074; | 0.6139         | 0.5207        | 6/10    | 0.6795  |
| NFE2L2 rs35652124; HMOX1 rs2071746; NOS3 rs207074; NOS3 rs1799983 | 0.6401         | 0.5807        | 10/10   | 0.2235  |

CVC, cross-validation consistency; GH, gestational hypertension; HP, healthy pregnant; PE, preeclampsia; NFE2L2, Nuclear Factor, Erythroid 2 Like 2; HMOX1, Hemeoxygenase 1; MDR, Multifactor dimensionality reduction; *p-value after 1.000 permutations

Table S3  Robust MDR interaction model among the NFE2L2, HMOX1 and NOS3 polymorphisms in PE patients classified as nonresponsive and responsive to total antihypertensive therapy

| Interaction Models                  | Training score | Testing score | CVC     | p-value |
|-------------------------------------|----------------|---------------|---------|---------|
| NOS3 rs1799983                      | 0.6383         | 0.6288        | 10/10   | –       |
| NOS3 rs2070744; NOS3 rs1799983       | 0.6631         | 0.6321        | 7/10    | 0.1155  |
| NFE2L2 rs35652124; NOS3 rs2070744; NOS3 rs1799983 | 0.6692         | 0.5870        | 9/10    | 0.3825  |
| NFE2L2 rs35652124; HMOX1 rs2071746; NOS3 rs2070744; NOS3 rs1799983 | 0.5412         | 0.4805        | 10/10   | 0.8870  |

CVC, cross-validation consistency; GH, gestational hypertension; HP, healthy pregnant; PE, preeclampsia; HMOX1, Hemeoxygenase 1; MDR, Multifactor dimensionality reduction; NFE2L2, Nuclear Factor, Erythroid 2 Like 2; NOS3, ....; *p-value after 1.000 permutations
Supplementary Fig. S1 Schematic diagram of the study workflow.

Supplementary Fig. S2 Plasma HO-1 levels in healthy pregnant women (A and B) and patients with preeclampsia (C and D) grouped according to the genotypes for the NFE2L2 polymorphism (A and C) and HMOX1 polymorphism. The bars show the boxplot indicates median [min – max].
Supplementary Fig. S3 Plasma HO-1 levels in patients with preeclampsia grouped according to the genotypes for the NFE2L2 polymorphism and responsiveness to methyldopa (responsive A and nonresponsive B) or total antihypertensive therapy (responsive C and nonresponsive D). The bars show the box plot indicates median [min – max].