RENAL INJURY DURING PRECLAMPSIA: ROLE OF EXTRACELLULAR VESICLES

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Definition of AKI in pregnancy: role of preclampsia;

New insights into the pathogenic mechanisms of endothelial injury during preclampsia: focus on glomerular damage and proteinuria;

Definition and characterization of circulating plasma Extracellular Vesicles (EV) in preclampsia and their role in glomerular injury,

Development of new potential therapeutic approaches.
• Definition of AKI in pregnancy: role of preclampsia;

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• Development of new potential therapeutic approaches.
Summary of renal hemodynamic and metabolic adaptations to normal human pregnancy

Length of both kidneys increase by 1 cm

Dilatation of calyceal system, renal pelvis and ureters

GFR and renal blood flow increase by 30-45%

Crs fall to 0.4-0.8 mg/dl so Crs of 1 mg/dl in pregnant should be considered as abnormal value

Excretion of glucose, protein and bicarbonate increase during pregnancy
Main causes of pregnancy-related acute kidney injury with overlapping clinical features

The timing of Pr-AKI also gives significant clues for etiology. Pr-AKI in the first trimester usually results from septic abortions (in developing countries) and prerenal azotemia from hyperemesis gravidarum. Most Pr-AKI episodes occur in the third trimester or closer to delivery and offer a larger differential: preeclampsia and hemolysis elevated liver function test and low platelet (HELLP) syndrome; thrombotic microangiopathies, namely thrombotic thrombocytopenic purpura (TTP)/atypical hemolytic uremic syndrome (aHUS); acute fatty liver of pregnancy (AFLP); severe hemorrhage, such as abruptio placentae; or puerperal sepsis. Both preeclampsia/HELLP and aHUS can extend to the postpartum period, with a higher frequency in the latter.
American College of Obstetrics and Gynecology definitions for preeclampsia

- Maternal blood pressure $\geq 140/90$ mm Hg on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously measured normal blood pressure
- Maternal blood pressure $\geq 160/110$ mm Hg: hypertension can be confirmed within a short interval (min) to facilitate timely antihypertensive therapy. And one of the following:
  - Proteinuria: $\geq 300$ mg in a 24-h urine collection
  - Protein/creatinine ratio $\geq 0.3$
  - Dipstick reading of 1+ (used only if other quantitative methods are not available)
  - Thrombocytopenia: platelet count $< 100,000$/mL
  - Renal insufficiency: serum creatinine concentrations $\geq 1.1$ mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
  - Impaired liver function: elevated blood concentrations of liver transaminases to twice the normal concentrations
  - Pulmonary edema
  - Cerebral or visual symptoms

Preeclampsia offers a unique window of opportunity to identify maternal endothelial dysfunction and preexisting cardiovascular disease.

It remains an underrecognized cause of cardiovascular and kidney disease in women and represents the confluence of preexisting vascular risk factors with superimposed endothelial injury from placental mediated antiangiogenic factors.

Future studies in cardiovascular risk modification in this phenotype of disease are essential to reduce the burden of cardiovascular disease in women.

A deeper understanding of the feto-placental-maternal interface will help delineate the biological aspects of future cardiovascular disease in these women and their offspring.
Among hypertensive disorders, pre-eclampsia (PE) is a frequent cause of maternal death and of complications for the newborns.


At the basis of PE there would be a placentation defect which would result into an altered perfusion with placental hypoxia, ischemic damage, syncytiotrophoblast apoptosis and release in the maternal circulation of antiangiogenic, vasoconstrictive factors........

(Roberts JM et al. 2009; Timofeeva AV et al. 2018)
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Aberrant placentation and angiogenesis in preeclampsia.

In normal pregnancy, cytotrophoblasts of fetal origin invade the maternal spiral arteries and replace endothelial cell layer. This action converts the spiral arteries from narrow highly resistant vessels to high-caliber capacitance vessels, which are capable of providing sufficient blood and nutrition supply to the fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial to an endothelial phenotype, a process referred to as pseudovasculogenesis, or vascular mimicry.

In preeclampsia, cytotrophoblasts fails to acquire invasive endothelial phenotype features, thus the invasion of the spiral arteries is inadequate leaving them narrow and highly resistant.
Summary of a current view of pathogenesis for preeclampsia
Summary of the pathogenesis of preeclampsia
C, On electron microscopy, note glomerular basement membrane (arrows) and marked reduction of capillary lumen (CL) caused by swollen endothelial cell cytoplasm.
Under physiological conditions in healthy pregnant women, podocytes and glomerular endothelium maintain a symbiotic process through the production and action of VEGF. This acts on podocytes and on glomerular endothelial cells through VEGFR-1 and VEGFR-2 respectively; by maintaining the correct function of these cells and preventing the production of ET-1 from glomerular endothelium, the ET-1 receptor remains unoccupied in podocytes.

These conditions will prevent loss of proteins to urine (Panel A). In women with PE the placenta is the principal source of sFlt-1 that is released into maternal circulation and reaches the glomerulus; once within the glomerulus the sFlt-1 binds and antagonizes free VEGF. This would lead to interruption of the VEGF podocyte autocrine loop and glomerular endothelium activation; this results in endothelial release of ET-1 that would cause nephrin shedding and lead to actin alterations in podocytes.
Downregulation of nephrin and synaptopodin may cause podocyte dysfunction and proteinuria in preeclampsia.
Preeclampsia: Novel Mechanisms and Potential Therapeutic Approaches

Zaher Armaly, Jimmy E. Jadaon, Adel Jabbour and Zaid A. Abassi

CVD death Kaplan–Meier survival according to gestational timing of preeclampsia. Survival analysis is based on 14, 403 pregnant women. A total of 481 had observed preeclampsia, and 266 died from cardiovascular disease and Cumulative risk of end-stage renal disease (ESRD) after first preeclampsia.

Sex in basic research: concepts in the cardiovascular field

Renée Ventura-Clapier, Elke Dworatzek, Ute Seeland, Georgios Kararigas, Jean-François Arnaí, Sandra Bruneleschi, Thomas C. Carpenter, Jeanette Erdmann, Flavia Franconi, Elisa Giannetti, Marek Gleberman, Susanna M. Hofmann, Claudine Junien, Miyuki Katai, Karolina Kubicki, Inke R. König, Gregor Hajdíc, Walter Malorni, Christin Mieth, Virginia M. Miller, Rebecca M. Reynolds, Hiroaki Shimokawa, Cara Tannenbaum, Anna Maria D’Ursi, and Vera Regitz-Zagrosek.
OUTLINE

• Definition of AKI in pregnancy: role of preclampsia;

• New insights into the pathogenic mechanisms of endothelial injury during preclampsia: focus on glomerular damage and proteinuria;

• Definition and characterization of circulating plasma Extracellular Vesicles (EV) in preclampsia and their role in glomerular injury;

• Development of new potential therapeutic approaches.
Exosomes have an endosome origin and are a rather homogenous population with a size ranging from 30 to 120nm.

They are released by exocytosis through a mechanism dependent on cytoskeleton activation and under the regulation of p53 protein.
**PRODUCTION OF MICROVESICLES**

- **Shedding vesicles** are usually larger than exosomes with size ranging from 100nm to 1µm.

- Formation of shedding vesicles takes place from the budding of small cytoplasmic protrusions followed by their detachment from the cell surface dependent on calcium influx, calpain and cytoskeleton reorganization.
  
  - The intra-cellular levels of calcium ions modify the asymmetric phospholipids distribution of plasmamembranes by specific enzymes named flippase, floppase and scramblase.
  
  - The increase of calcium ions inhibits translocase and induces activation of scramblase that translocates phosphatidylserine from the inner leaflet of the cell membrane bilayer to the outer with changes in curvature-mediated lateral redistribution of membrane components with the formation of membrane nanodomains.

- Calcium ions by activation of calpain which cleaves tallin and activin, and of gelsolin which cleaves actin-capping proteins also favor the reorganization of cytoskeleton.
D. **EV may mediate a horizontal transfer of genetic information.**

- **EV derived from murine embryonic stem cells induce an epigenetic reprogramming of haematopoietic stem/progenitor cells.**

- **EV derived from human endothelial progenitor cells activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA.**
First-trimester trophoblast cells act as environmental sensors. These cells may respond to environmental flux, such as changes in the glucose and oxygen concentrations, by synthesizing and releasing exosomes based on the particular environmental conditions.

Trophoblast-derived exosomes have multiple effects on target cells, including induction of cell migration, apoptosis, and proinflammatory cytokine release. Increased exosome release from trophoblast cells in response to environmentally challenging conditions including elevated glucose concentrations and low oxygen tension may disrupt the Th1/Th2 Th17/Treg cytokine balance.
Role of EVs in pathogenesis of preeclampsia

Endothelial dysfunction worsens with advancing gestation as the mother is unable to adapt to the physiological stress of pregnancy.

Placental preeclampsia is commonly viewed as early or severe, while maternal preeclampsia is sometimes characterized as late or mild.

Maternal risk factors and placental abnormalities cause systemic maternal cell activation resulting in release of EVs.

Endothelial-, leukocyte-, and platelet-derived EVs give rise to vascular dysfunction, immune modulation, and increased thrombotic propensity.

These processes collectively contribute to progression of pathogenesis of preeclampsia.
AIMS

TO ISOLATE AND CHARACTERIZE EV FROM PE PATIENTS (MODERATE VS. SEVERE FORMS COMPARED WITH HEALTHY PREGNANCY) (N=20).

TO EVALUATE THE BIOLOGICAL EFFECTS OF PRECLAMPTIC PLASMA EV ON HUMAN KIDNEY-DERIVED GLOMERULAR ENDOTHELIAL CELLS AND PODOCYTES.
1. **DEMOGRAPHIC FEATURES AND OBSTETRIC ANAMNESIS** (patients and controls)

2. **CLINICAL MEASUREMENTS PE PATIENTS** (systolic and diastolic arterial blood pressure; urine creatinine and uric acid; 24 h proteinuria; liver function; emocrome) at diagnosis (t0), delivery (T1) and one month after delivery (T2)

3. **BLOOD SAMPLING** for MVs isolation at T0, T1 T2 in PE patients and at T1 and T2 for controls
RESULTS

CLINICAL FEATURES

<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia (n 20)</th>
<th>Controls (n 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32 (26-41)</td>
<td>32.6 (21-42)</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian 13 (68.4%)</td>
<td>Caucasian 17 (85%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>African 4 (21.2%)</td>
<td>Asiatic 2 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Southamerican 1 (5.2%)</td>
<td>African 1 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>South East Asia 1 (5.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.5 (17-34)</td>
<td>25.3 (18-29)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Ex</td>
<td>1 (5,2%)</td>
<td>2 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Never</td>
<td>2 (10,5%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (82.3%)</td>
<td>16 (80%)</td>
<td></td>
</tr>
<tr>
<td>Alcool</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Drugs assumption</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic therapy</td>
<td>4 (21%)</td>
<td>2 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (10.5%)</td>
<td>2 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>2 (10.5%)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

No patients/controls suffer from CKD, autoimmune and endocrine diseases, diabetes.

No antiaggregant therapy
## RESULTS

### CLINICAL PARAMETERS OF PE PATIENTS AT DIFFERENT TIME POINTS

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>Delivery</th>
<th>1 month after delivery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAP mmHg</strong></td>
<td>149.2 (140-160)</td>
<td>145.8 (140-170)</td>
<td>126 (110-150)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>DAP mmHg</strong></td>
<td>98.6 (90-100)</td>
<td>92.6 (90-100)</td>
<td>78 (60-100)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Proteinuria g/die</strong></td>
<td>1.7 (0.3-4.2)</td>
<td>0.7 (0.12-2.1)</td>
<td>0.32 (0.1-0.7)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>AKI</strong></td>
<td>3 (STAGE 1 KDIGO)</td>
<td>0</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Hb g/dL</strong></td>
<td>11.4 (9-12)</td>
<td>10.5 (6.5-14.2)</td>
<td>11.4 (10.7-11.5)</td>
<td>NS</td>
</tr>
<tr>
<td>*<em>PTLs <em>10 ³ mm3</em></em></td>
<td>212833.3 (114000-280000)</td>
<td>190842.1 (51000-384000)</td>
<td>236333.3 (160000-367000)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>AST U/L</strong></td>
<td>179 (8-470)</td>
<td>141.2 (14-1146)</td>
<td>20.3 (15-25)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>ALT U/L</strong></td>
<td>74.8 (7-519)</td>
<td>144.8 (9-1133)</td>
<td>21.3 (20-25)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Uric acid mg/dl</strong></td>
<td>6.1 (4.2-7.6)</td>
<td>5.8 (3.8-7.7)</td>
<td>4.1 (3.5-5.5)*</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SAP: systolic arterial pressure; DAP: diastolic arterial pressure; AKI: acute kidney injury; PLTs: platelets
EV ISOLATION AND CHARACTERIZATION

Prior to the isolation procedures of EV from human plasma, samples were submitted to two centrifugations at 3,000g for 20 min to remove cell debris and other contaminants. EV were purified as previously described by Théry et al. and re-suspended in the appropriate buffer to study biological activities or in lysis buffer for further studies (RNA extraction and western blot analysis).

NanoSight NS300 was used to analyze the concentration and size distribution of EV by means of the NTA software.

EV characterization was performed through membrane proteins profile analysis by using flowcytometry to identify the possible tissue of origin. CD105, CD81, CD63, CD4, CD42b, CD90, PLAP markers, were analyzed.
EV CHARACTERIZATION

EV SIZE AT DIFFERENT TIMING

NO SIGNIFICANT DIFFERENCES IN EV SIZE IN PE AT DIFFERENT TIMING

AT DELIVERY, IN PE EV SIZE IS HIGHER THAN IN CONTROLS
**EV CHARACTERIZATION**

**EV CONCENTRATION AT DIFFERENT TIMING**

Mean MV concentration at different time points

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Preeclampsia</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>8.653 e+011 particles/ml</td>
<td>/</td>
</tr>
<tr>
<td>1 month after delivery</td>
<td>7.408 e+011 particles/ml</td>
<td>7.11 e+011 particles/ml</td>
</tr>
</tbody>
</table>

NO SIGNIFICANT DIFFERENCES BETWEEN PE AND CONTROLS, IN GENERAL…BUT……

…EV CONCENTRATION IS HIGHER IN SEVERE PE IN COMPARISON WITH MILD PE AT BOTH DELIVERY AND AT 1 MONTH AFTER DELIVERY. IN SEVERE PE EV CONCENTRATION AT DELIVERY IS HIGHER THAN IN CONTROLS.
CORRELATION BETWEEN EV CONCENTRATION AND CLINICAL VARIABLES OF SEVERE PE AT DIAGNOSIS

**Linear correlation between EV and uricemia at diagnosis**

- Pearson $r$: 0.8728
- 95% confidence interval: 0.4955 to 0.9729
- $R^2$: 0.7613
- $P$ value (one-tailed): 0.0011
- Significant? ($alpha = 0.05$): Yes
- Number of XY Pairs: 9

**No correlation between EV and proteinuria at diagnosis**

- Pearson $r$: -0.5157
- 95% confidence interval: -0.8789 to 0.2259
- $R^2$: 0.2660
- $P$ value (one-tailed): 0.0776
- Significant? ($alpha = 0.05$): No
- Number of XY Pairs: 9
CORRELATION BETWEEN EV CONCENTRATION AND CLINICAL VARIABLES OF SEVERE PE AT DELIVERY

**LINEAR CORRELATION BETWEEN MVs AND PROTEINURIA AT DELIVERY**
EV from PE are PLAP+ both at diagnosis and delivery

The concentration of PLAP+ EV is higher in severe PE in comparison with mild PE

Severe PE women have higher PLAP+ EV concentration 1 month after delivery in comparison with the other groups
CHARACTERIZATION OF PLASMA EV CELLULAR ORIGIN IN PE vs. HEALTHY CONTROLS

In PE, EV derived from leukocytes, platelets and endothelial cells are higher in comparison with controls.

In severe PE those markers are higher than in mild PE
BIOLOGICAL EFFECTS OF PRECLAMPTIC PLASMA EV ON GLOMERULAR ENDOTHELIAL CELLS: IN VITRO STUDIES

EV

Endothelial cells

Podocytes
EFFECTS OF PLASMA EV ISOLATED FROM DIFFERENT GROUPS ON:
GLOMERULAR ENDOTHELIAL CELLS (LEFT PANEL)
PODOCYTES (RIGHT PANEL)

* p<0.05 vs healthy control
** p<0.05 between groups
# p<0.05 vs mild pathological
PLASMA EV EFFECTS ON CULTURED PODOCYTES

PERMEABILITY

NEPHRIN EXPRESSION
EXTRACELLULAR VESICLES IN PRECLAMPSIA:
ALTERATIONS OF THE PHYSIOLOGICAL ENDOTHELIAL-PODOCYTE CROSS-TALK IN GLOMERULI
OUTLINE

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• Definition and characterization of circulating plasma Extracellular Vesicles (EV) in preclampsia and their role in glomerular injury,

• Development of new potential therapeutic approaches: a) Apheresis/Sorbents; b) Complement inhibition; c) Stem cell therapy.
Innovative approach for the elimination of the elevated levels of sFlt-1 by apheresis for the management of preeclampsia.
SORBENT-BASED EXTRACORPOREAL THERAPIES FOR PLASMA EV REMOVAL

Removal of Soluble Fms-Like Tyrosine Kinase-1 by Dextran Sulfate Apheresis in Preeclampsia

Ravi Thadhani,* Henning Hagmann,† Wiebke Schaarschmidt,‡ Bernhard Roth,§ Tuelay Cingoz,‖ S. Ananth Karumanchi,¶ Julia Wenger,* Kathryn J. Lucchesi,* Hector Tamez,‖ Tom Lindner,‖ Alexander Fridman,‡ Ulrich Thome,§§ Angela Kribs,§ Marco Danner,§ Stefanie Hamacher,‖ Peter Mallmann,‖ Holger Stepan,‡ and Thomas Benzinger¶¶

*Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; †Renal Division and Department of Medicine and Center for Molecular Medicine, §Department of Neonatology, ‡Department of Obstetrics and Gynecology, ¶Institute of Medical Statistics, Informatics and Epidemiology, and ¶¶Cologne Excellence Cluster on Cellular Stress Response in Aging Associated Diseases, University of Cologne, Cologne, Germany; ‖Department of Obstetrics, ‖Division of Nephrology, Department of Internal Medicine, Neurology, and Dermatology, and ¶¶Department of Neonatology, University Hospital Leipzig, Leipzig, Germany; §Department of Medicine and Obstetrics and Gynecology, and **Department of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and ¶Howard Hughes Medical Institute, Chevy Chase, Maryland

Sorbent: Amberchrom CG-161 M resin (Rohm and Haas Company, Philadelphia, PA, USA)

Cantaluppi et al., Critical Care 2010
Complement activation and regulation

Targeting excessive complement activation, particularly the terminal complement complex (C5b-9) and C5a may be an effective strategy to prolong pregnancy in women with preeclampsia.

Continued research is needed to identify the initiator(s) of activation, the pathways involved and the key component(s) in the pathophysiology to allow development of safe and effective therapeutics to target complement without compromising its role in homeostasis and host defense.
Complement dysregulation and angiogenic imbalance are important mediators of disease in severe preeclampsia. Use of established biomarkers confirmed their relevance in active disease. While plasma complement and angiogenic markers do not correlate well in preeclampsia subjects, we found a strong relationship between the anti-angiogenic condition and urinary excretion of C5b-9. Detection of C5b-9 in the urine may correlate with glomerular or proximal tube injury in the kidney and may be an important marker for disease management and treatment.

Table 1: Plasma Angiogenic Factors in Relation to Urinary Detection of C5b-9 in All Subjects

<table>
<thead>
<tr>
<th>Plasma angiogenic markers</th>
<th>Plasma concentration (pg/mL)</th>
<th>Urine C5b-9 concentration (pg/mL)</th>
<th>Urinary excretion of C5b-9</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sFlt-1</td>
<td>4556 (3137-8165)</td>
<td>32,029 (16,437-59,725)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PIGF</td>
<td>226 (145-500)</td>
<td>15.6 (11.4-28.6)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>153 (129-218)</td>
<td>119 (102-131)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>bFGF</td>
<td>14.7 (9.7-24.9)</td>
<td>19.3 (14.9-34.0)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>
Both the CFU central and radial cells were >90% positive for Dil-Ac-LDL uptake and lectin surface staining, and this did not appear to differ by pregnancy outcome. The cells comprising CFUs were likewise >90% positive for the hematopoietic surface antigen CD45, the monocyte/macrophage antigen CD14, and macrophage antigen CD115.

Endothelial progenitor cells (EPCs) provide paracrine support to the vascular endothelium and may also replace damaged or senescent endothelial cells. Low numbers of endothelial progenitor colony-forming units (CFU-ECS) in culture are a predictive biomarker of vascular disease.

CFU-ECS derived from culture of peripheral blood mononuclear cells, a correlate of cardiovascular risk in nonpregnancy populations, are rarified in women with preeclampsia compared to normal pregnancy. PCR analysis is consistent with a maternal origin of these cells.
Transplantation of endothelial progenitor cells for improving placental perfusion in preeclamptic rats

Jianwen Zhu · Xiangwei Cheng · Qianhua Wang · Yan Zhou · Fang Wang · Li Zou

Transplantation of EPCs into placenta of preeclampsia model rats, urine protein and blood pressure of pregnant rats.

A pregnant rat with preeclamptic symptom was created by L-NAME injection and abdominal aortic constriction.

This operation successfully replicated preeclampsia pathological changes, such as intrauterine growth restriction of foetal rats, artery wall thickening of the glomerulus, luminal stenosis, and fibrin deposition, similar to human preeclampsia.

EPCs could effectively improve the symptom of preeclampsia in rats, thereby providing an potential method to clinically control preeclampsia.

Table 4 Blood pressure of pregnant rats (x ± s, mmHg)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Day after EPC transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7 days</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>98.3 ± 4.32</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>115.4 ± 2.63*</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>117.1 ± 4.28</td>
</tr>
</tbody>
</table>
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Thanks for the attention

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