Placental growth factor supplementation abolishes placental ischemia-induced hypertension

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Preeclampsia is diagnosed with the occurrence of the following symptoms at ≥ 20 weeks of gestation:

- New-onset hypertension (140/90mmHg) AND
- Proteinuria (>5g/24h or 3+ on dipstick) OR
  - Pulmonary edema
  - Oliguria (<400mL/24h)
  - Persistent headaches
  - Epigastric pain and/or impaired liver function
  - Thrombocytopenia
  - Oligohydraminos, decreased fetal growth, placental abruption
Why is it important to study the pathophysiology of preeclampsia?

• The pathophysiology is unclear

• The only ‘cure’ is early delivery of the fetus and placenta

• Worldwide, 10 million women develop preeclampsia per year killing 76,000 mothers and 500,000 babies per year

• In the US, within the past few decades, the rate of preeclampsia has increased 30% with an increased contribution to maternal death by 7.5%

The increasing prevalence of preeclampsia highlights the importance of understanding the pathogenesis of this disorder to develop novel target therapies
Linking placental ischemia with maternal hypertension

Abnormal placental vascular remodeling

Placental ischemia

Release of Placental Factors

Endothelial dysfunction and impaired renal function

Hypertension

Maternal Endothelial Activation

Placental villus

ET-1

NO

TNF-α

sFlt-1

AT1-AA

Hypertension
Circulating levels of the anti-angiogenic factor sFlt-1 are greater in women with preeclampsia

sFlt-1 is a soluble vascular endothelial growth factor (VEGF) receptor that antagonizes and reduces bioavailable VEGF and PlGF.

PlGF is a member of the VEGF sub-family that prevents VEGF from binding VEGFR1 therefore increasing VEGF signaling through VEGFR2.

Maynard et al, JCI 2003
Placental ischemia-induced hypertension in rats is accompanied by increased circulating sFlt-1 and reduced VEGF and PlGF in the circulation.

Gilbert et al, Hypertension 2007
It is unknown whether therapeutically increasing circulating PlGF levels could serve as a treatment strategy for reducing blood pressure in preeclampsia.
Hypothesis

PlGF supplementation prevents the development of placental ischemia-induced hypertension
Methods: A rat model to study the affects of Reduced Uterine Perfusion Pressure (RUPP)

Gestational day 14

Gestational day 19

Li et al. *AJP Heart Circ Physiol* 2012

Alexander et al. *Hypertension* 2001
**Methods**

### Gestational Day

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| Harlan Sprague-Dawley rats: Normal Pregnant (NP) OR RUPP ± 180 μg/kg/day rhPlGF, osmotic pump, ip | Carotid arterial catheters | 1. Blood pressure  
2. Pregnancy weights  
3. Plasma collected for [rhPlGF] |

4 groups:  
NP, N=11  
RUPP, N=15  
NP + PlGF, N=5  
RUPP + PlGF, N=12
Chronic rhPlGF infusion increases plasma rhPlGF levels in both NP and RUPP rats
Chronic rhPlGF infusion did not prevent RUPP-induced reductions in fetal weight

*P<0.05 vs. NP
Chronic rhPlGF infusion did not prevent RUPP-induced reductions in placental weight

*P<0.05 vs. NP
**Chronic rhPlGF infusion increased placental sufficiency only in RUPP rats**

Placental sufficiency = fetal weight/placental weight

†P<0.05 vs. NP and RUPP
Placental ischemia-induced hypertension is abolished following rhPlGF supplementation

*P<0.05 vs. NP
†P<0.05 vs. RUPP
Summary

- Chronic rhPlGF infusion increases plasma rhPlGF levels in both NP and RUPP rats

- Chronic rhPlGF infusion does not prevent RUPP-induced reductions in fetal or placental weights, but increased placental sufficiency only in RUPP rats

- Placental ischemia-induced hypertension is abolished following rhPlGF supplementation
Conclusions

Maternal Hypertension

Placental Ischemia

↑ Placenta & Plasma sFlt-1

↑ Plasma PIGF

↑ Plasma VEGF

↓ Endothelin-1, ↑ Nitric Oxide

↓ Maternal Hypertension

rhPlGF
Perspectives

Therapeutically increasing PlGF levels could potentially serve as a novel treatment strategy for preeclampsia
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