Case presentation

- 19 yo Hispanic female @ 33+ 0 weeks of gestation
- Presenting to the OB clinic for routine follow-up
- Found with:
  - BP 145/98
  - Leg swelling
  - Urine dipstick with 3+ protein
- BP normal, normal UA 2 months prior
HPI

- c/o occasional mild headaches x 3 weeks, no vision changes
- Leg edema
- Fatigue
ROS

- Constitutional: *fatigue*, no fever, chills
- HEENT: *headaches +*, no vision changes
- Respiratory: no shortness of breath, no cough
- Cardiac: Negative for chest pain, orthopnea and palpitations
- GI: Negative for abdominal pain, change in bowel habits, nausea, vomiting
- GU: Negative for dysuria, frequency, hematuria, frothy urine
- MSK: *+ Leg swelling*, negative for arthralgia, back pain
- Skin: no skin rashes
History Contd..

- **PMH:** None
- **PSH:** Appendectomy at age 12
- **Meds:** Prenatal vitamins
- **Allergies:** NKDA
- **SH:** Cashier, alcohol socially, no smoking or drug use
- **FH:** Father with DM2, no h/o HTN, renal disease, preeclampsia
Physical Exam

- **Vitals**: afebrile, HR 75, **BP 140/91**, sat 100% on RA
- **General**: NAD, pleasant, comfortable
- **HEENT**: moist mucos membranes
- **CVS**: S1S2 normal, **flow murmur** over LLSB
- **Pulmonary**: CTABL, no wheezing, no crackles
- **Abdomen**: gravid abdomen, soft, non tender
- **Ext**: lower extremity non pitting edema to shin, 1-2+ pitting edema of foot
Labs

LFTs: AST/ALT: 21/14, ALP 214, T bil 0.4, **Albumin 3.1**
Lipid: HDL 54, Chol 198, **TG 459**
Uric Acid 6.8
LDH 183

- **UA**: neg glucose, neg ketones, SG 1.010, **2+ Blood**, **4+ Protein**, neg nitrite, neg leuk esterase
- Urine Micro: few RBCs, squamous epithelial casts
- Urine Protein/Cr: **8.3 gm/gm**
Differentials

- Preeclampsia
- SLE
- Membranous
- Minimal Change Disease/ IgA
Additional Labs/Imaging

- Renal US: normal sized kidneys, no hydro or calculi
- HIV neg
- HepB panel neg
- ANA: neg C3/C4: normal
Hospital Course

- Received dexamethasone for fetal lung maturity, nifedipine for tocolysis
- Continuous feto maternal monitoring
- BP elevated to 160-170s/100-110s, worsening of edema
- Baby delivered on hospital D6 at 33+ 6 weeks
Follow Up at Renal clinic: 1 month later

BP 113/73, no edema

Lipid: HDL 41, Chol 216, TG 614

UA: no blood protein 3+, small LE, wbc 2-5

Uprot/Ucr: 3.7 gm/gm

Ca: 9.5
Introduction

- Characterized by new-onset hypertension and proteinuria at ≥20 weeks of gestation

- In the absence of proteinuria, diagnosis requires HTN + e/o systemic disease (viz thrombocytopenia, elevated liver transaminases, renal insufficiency, pul. edema and visual or cerebral disturbances)

- Affects 3–5% of all pregnancies, and is a leading cause of maternal and perinatal morbidity and mortality

- Can progress to eclampsia, which is characterized by new-onset grand mal seizures and affects 2.7–8.2 women per 10,000 deliveries

Eclampsia was first recognized as a convulsive disorder of pregnancy

Greek word *eklampsis* (meaning lightning), reflecting the sudden onset of convulsions in pregnant women

1840: Albuminuria was reported in patients with eclampsia and approx 50 years later, presence of HTN recognized in such patients

The term pre-eclampsia was subsequently introduced to describe the state preceding eclampsia

The prevention of eclampsia was proposed as a major goal of prenatal care in 1901, which led directly to the current emphasis on detecting early signs of pre-eclampsia.

*Lindheimer Seminar on History. The History of Preeclampsia and Eclampsia as Seen by a Nephrologist (2012)*
Risk Factors

**Box 1 | Risk factors for pre-eclampsia**

- Nulliparous women
- Extreme maternal age (<20 years\(^{193}\) or >35 years\(^{194}\))
- History of pre-eclampsia in previous pregnancy
- Multi-fetal gestation
- Obesity\(^{195,196}\)
- Family history of pre-eclampsia (mother or sister)
- Pre-existing medical conditions, including chronic hypertension, diabetes mellitus, antiphospholipid syndrome,\(^{197,198}\) thrombophilia, autoimmune disease, renal disease, infertility
- Limited sperm exposure
- ‘Dangerous father’\(^{28,199}\)
- Urinary tract infection\(^{191,200}\)
Pathogenetic Mechanisms

- Uterine blood flow increases to enable perfusion of the intervillous space of the placenta and to support fetal growth

- Achieved by physiological transformation of the spiral arteries of the uterus

- Trophoblasts invade the arterial wall, destroy the media and transform the spiral arteries from narrow-diameter to large-diameter vessels
Pathogenetic Mechanisms

Normal pregnancy vs. Pre-eclampsia:
- **Maternal blood flow**
- **Spiral artery**
- **Trophoblast**

In normal pregnancy, maternal blood flows through the spiral artery without obstruction. In pre-eclampsia, there is an obstruction, indicated by the increased blood flow and the presence of trophoblast, leading to a pathological condition.
Pathogenetic Mechanisms
Pathogenetic Mechanisms

Familial clustering

- Twin studies: heritability 22% -47%

- Candidate-genes: Mat: COL1A1, IL-1α (IL1A), Fetal: PLAUR

- Mat–fetal genotype incompatibility of lymphotoxin-α (LTA), VWF and COL4A2

- DNA variants: Factor V Leiden mutation, mutations in e NOS, HLA and angiotensin-converting

- SNP rs1799889 in SERPINE1
- **Trophoblasts**: Initial placentation under relative hypoxia (HIF –α). Persistent hypoxia or failure to downregulate TGF-β3 expression > 9 wks : failure of proliferative to invasive

- **Decidual defect**: optimal preconditioning , successive menstruations

- **Combination of factors:**
  - Maternal–fetal immune recognition at the site of placentation.
  - HLA-C (C1 and C2) molecules of trophoblasts and receptors KIRs (A and B) of uterine NK cells
  - Uterine NK cells release chemokines, angiogenic factors and cytokines that promote trophoblast invasion, incr upon binding of HLA-C to stimulatory KIRB, reduced by Ag binding to KIRA. KIR BB mothers carrying HLA-C1 fetuses might have the best chance of adequate placentation
– Intermittent hypoxia and re-O2, probably from deficient conversion of the myometrial segment of the spiral arteries → Oxidative stress

– Protein carboxylation, lipid peroxidation and DNA oxidation

– **Sources:**
  - Xanthine DH to XO promotes the production of uric acid and superoxide from degraded purines
  - Free heme, hemoxygenase
- Normal reduced vascular responsiveness to Ang II vs inc sensitivity in preeclampsia
- A subset of women with pre-eclampsia have detectable serum autoantibodies against (AT1)
- Activate AT1 in endothelial cells, vascular smooth muscle cells and mesangial cells

- In pregnant rats, anti-AT1 autoAbs
  - HTN, proteinuria, GC endotheliosis and incr production of sVEGFR and s-endoglin
  - ROS, stimulates NADPH oxidase
  - stimulate tissue factor release by monocytes and vascular smooth muscle cells
  - Collectively, lead to increased thrombin generation, impaired fibrinolysis and fibrin deposition.
Narrow spiral arteries create conditions for ischemia–reperfusion injury in the intervillous space.

During states of energy crisis (such as hypoxia), the ER suspends protein folding (UPR).

UPR can lead to cessation of cell proliferation and, when severe, apoptosis.

Trophoblast apoptosis \(\rightarrow\) release of microparticles and nanoparticles into the maternal circulation \(\rightarrow\) stimulate intravascular inflammatory response.
**Antiangiogenic Factors: sFlt**

- **sFlt** (soluble fms-like tyrosine kinase- splice variant of the VEGF receptor flt-1, lacking the transmembrane and cytoplasmic domains)

- Antagonist to VEGF and PlGF by adhering to their receptor-binding domains, preventing their interaction with endothelial receptors on the cell surface and thereby inducing endothelial dysfunction

- 6 immunoglobulin like domains:
  - 2\textsuperscript{nd} immunoglobulin-like domain makes up its ligand (VEGF and placental growth factor) binding site
  - Heparin- and matrix-binding domain located in the 3rd immunoglobulin-like domain that is distinct

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*Thadani et al. Circulation. 2011*

*Karumanchi et al. J. Clin. Invest 2003*

*Karumanchi et al N Engl J Med 2004*
Excess placental (sFlt1) may contribute to endothelial dysfunction, HTN, and proteinuria in preeclampsia

• AIM: Determine if expression of sFLT-1 mRNA and serum sFlt-1 levels higher in preeclamptic vs. control women

• Methods:
  • 4 samples from the placentas of women with mild and severe preeclampsia vs control, Northern blot done
  • Serum was collected from pregnant women at delivery and 48 hours after delivery

Determine if sFlt-1 impairs angiogenesis

- Human umbilical vein endothelial cells were treated with 5% patient serum, plated, and incubated to assess for tube formation.

Determine if sFlt-1 can cause HTN and proteinuria in vivo

- Recombinant adenovirus with sFlt-1 injected into the tails of pregnant (VEGF and PLGF) and non-pregnant rats (VEGF only)
  - Both groups of rats developed proteinuria and HTN

- Adenovirus containing Flk1, which only antagonizes VEGF, was then injected into the tails of pregnant and nonpregnant rats.
  - Pregnant rats did not develop HTN and proteinuria (PLGF not affected), vs nonpregnant rats did (absence of PLGF)

Antiangiogenic Factors: soluble Endoglin

- Antiangiogenic protein that may inhibit TGF-B1 signals in the vasculature

- Prevents binding of TGF-B1 to its receptors and downstream signaling, including eNOS

- Venkatesh and Karumanchi et al demonstrated
  - Soluble eng x 4 times higher in preeclamptic patients
  - Soluble Eng elevated x 5 in severe preeclamptics and x 10 in patients with HELLP
  - sEng increased capillary permeability

The degree of uterine ischemia is determined by the severity of the placentation defect and fetal demand on the blood supply.

The timing and extent of the mismatch determines the clinical presentation (fetal death, pre-eclampsia with IUGR, IUGR alone and late pre-eclampsia).

Pre-eclampsia: adaptive responses involving the release of inflammatory cytokines, anti-AT1 autoantibodies, angiogenic and antiangiogenic factors and syncytiotrophoblast-derived particles into the maternal circulation.

These factors induce leukocyte activation, intravascular inflammation, endothelial cell dysfunction and excessive thrombin generation.

The multi-organ features of pre-eclampsia result from the consequences of these processes in different target organs.

Figure 1. Summary of the pathogenesis of preeclampsia.

Karumanchi et al. Advances in CKD, May 2013
Main Clinical Manifestations

- HTN
- Proteinuria
- Reduced GFR

CJASN 2007
Nat Rev 2014
Hemodynamic Changes in Normal Pregnancy

- Increase in cardiac output
- Expanded circulatory volume
- Decrease in peripheral vascular resistance
- Overall minimal change in systolic pressure but more pronounced change in diastolic pressure
HTN: Vasoconstriction

Relaxin, upregulates NOS, which generates NO from arginine, via the endothelial endothelin B receptor

Vasoconstrictors:
- In preeclampsia, predominance of vasoconstrictors (endothelin, thromboxane A2) over vasodilators (NO, prostacyclin).
- Asymmetric dimethyl arginine, which inhibits nitric oxide synthase, is higher in patients with pre-eclampsia.

Increased sensitivity to RAS: During pregnancy the RAS is upregulated, but there is resistance to its pressor effects.
- One reason may be the high levels of Ang(1-7), which inhibits angiotensin II.
- In pre-eclampsia, the levels of ang(1-7) are lower.
- IgG antibody to AT-1 in a subset of pre-eclamptic patients

sFlt and soluble Eng prevent vasodilation normally seen in pregnancy.

CJASN 2007
Nat Rev 2014
Proteinuria

Renal biopsies from women with preeclampsia show glomerular endotheliosis (GEN)
- obliteration of endothelial fenestrae, endothelial edema, and obliteration of the capillary space

Strevens et al. demonstrated this lesion was present in preeclampsia, gestational HTN without proteinuria and also in normal pregnant women

Mere endothelial lesion is not sufficient to explain the loss of filtration function

Proteinuria: Role of anti VEGF

Eremina et al NEJM 2008

- 6 patients Rxed with bevacizumab, → glomerular disease characteristic of TMA
- Created podocyte specific VEGF KO mice
Results

Albuminuria at 4 weeks of Doxy induction

ESRD like picture at 9 weeks
Results
Proteinuria

Critical role of impaired VEGF signaling within the glomerulus in the pathogenesis of TMA/proteinuria

Low VEGF and high concentrations of sFlt-1, may alter podocytes by two different mechanisms

- sFlt-1 interrupts VEGF flow from the podocyte to the endothelium in an indirect manner
  → Injured endothelium produces endothelin-1 → toxic effect on the podocyte → damage → proteinuria
- sFlt-1 can directly disrupt the autocrine loop for podocyte-derived VEGF

Emrina et al NEJM 2008
Reduced GFR

In normal pregnancy, glomerular hyperfiltration occurs by 40 to 60% compared to non gravid state

- due depression of the plasma oncotic pressure (GC) in the glomerular capillaries resulting from
- hypervolemia-induced hemodilution that lowers the protein concentration of plasma that enters the glomerular microcirculation
- Elevated rate of RPF

Decrease in GFR is seen in preeclampsia

Compared 13 normotensive pregnant white women to 10 preeclamptic women

Methods

At 36-38 weeks
- 24 hour urine for protein
- CBC, BMP
- Infused with dextran-40 (neutral molecule), inulin, and PAH.

1 hour later the subjects voided

- Calculation of the RPF, the GFR, and the FF.
- Mathematical models were used to calculate Kf and pi Gc
- Dextran molecules were separated by chromatography in the urine by size to determine size selectivity.
Results: Moran et al

– Compared to normal pregnancy, preeclamptic did not show a rise in RPF, showed a 50% reduction in Kf, and a decrease in passage of 31-63 Angstrom dextrans

– 5 months postpartum the experiment was repeated in normal and preeclamptic women, and there was no difference
Diagnosis

**Clinical:**
- BP ≥140/90 mmHg X 2, at least 4 h apart or ≥160/110 mmHg within a shorter interval (minutes), at ≥20 weeks, in women with previously normal BP and proteinuria
- In the absence of proteinuria, new-onset HTN plus new onset of any
  - Cr >97 μmol/l or doubling in the absence of other renal disease
  - Elevation of liver transaminases to twice normal concentration
  - Pulmonary oedema; and cerebral or visual symptoms

**Atypical:** HELLP

**Serologic:**
- Levels of sFlt
- Levels of soluble endoglin

Biomarkers for prediction

Some evidence suggests benefit from early (<16 weeks) administration of aspirin or combinations of NO donors and antioxidants

- Placental morphology and/or perfusion
- Uterine artery Doppler velocimetry (UtADV) in the first or second trimesters

Figure 1 | Uterine artery Doppler velocimetry findings in the second trimester of pregnancy. a | Normal findings. b | Abnormal findings, indicated by either the presence of bilateral uterine artery early diastolic notches (arrows) or a mean pulsatility index (calculated as [peak systolic velocity – end diastolic velocity]/time averaged velocity, averaged across both uterine arteries), above the 95th percentile for gestational age.
Biomarkers for prediction

Kuc et al 2007: Systematic review, combinations of ≥ 2/7 serum biomarkers:
- A disintegrin and metalloproteinase domain-containing protein 12 (ADAM 12), free CG-β, inhibin A, activin A, PP13, placental growth factor (PIGF) and PAPP-A in the first trimester identified 55–75% of patients with early pre-eclampsia (delivery <34 weeks) and 30–40% of all patients with pre-eclampsia, with a false-positive rate of 10%.

Chaiworapongs a et al. 80–90% of women with preterm pre-eclampsia and 40–50% of those with pre-eclampsia at term have abnormal plasma PIGF:sVEGFR-1 or PIGF:soluble endoglin ratios, (defined as being < 10th percentile for gestational age of uncomplicated pregnancies) within the 7 days prior to delivery.

Prevention of Preeclampsia

A broad range of interventions has been tested

- **Antiplatelet agents**
  - An imbalance between prostacyclin and thromboxane

  - Multicentre RCT of low-dose aspirin for the prevention and treatment of pre-eclampsia in 9,364 pregnant women, the use of aspirin was a/w a non-significant reduction (12%) in the incidence of proteinuric pre-eclampsia

  - Meta-analysis of 32,217, aspirin prophylaxis had a significant (10%) reduction in the incidence of pre-eclampsia, preterm birth (<34 weeks of gestation) and a composite of serious adverse pregnancy outcomes
Antioxidants

- meta-analysis of RCTs of vitamins C and E failed to show a beneficial effect for preventing pre-eclampsia

- pre-eclampsia was reduced by 63% in patients at risk (due to personal or family history of pre-eclampsia) receiving l-arginine (5.4 g daily) + vitamin C (500 mg daily) and vitamin E (400 IU daily) < 24 weeks of gestation

Calcium supplementation

- RCT from US: 4,589 pregnant women, calcium (2 g daily) vs placebo
  - No significant reduction in the incidence or severity of pre-eclampsia, or delay in its onset

- Cochrane systematic review and meta-analysis: women who received calcium (≥1 g daily) had a reduced incidence of pre-eclampsia (RR 0.45, 95% CI 0.31–0.65)
  - Beneficial effect was greatest for patients with low baseline calcium intake (RR 0.36, 95% CI 0.20–0.65), and high risk of pre-eclampsia (RR 0.22, 95% CI 0.12–0.42).
Reverse the imbalance of angiogenic and antiangiogenic factors: proposed mechanisms

- Statins have the potential to reverse the angiogenic imbalance through their pleiotropic effects (stimulating trophoblast production of PlGF, improving endothelial function, upregulating HO 1, decreasing oxidative stress or inflammation)

- Administration of VEGF\textsuperscript{121} or extracorporeal removal of soluble VEGFR-1 (sVEGFR-1)
Treatment

Control of HTN: ≥160/ ≥110 to prevent hemorrhagic stroke and to maintain uteroplacental perfusion

Indications for delivery

- Gestational age 37 weeks
- Worsening of maternal or fetal conditions
- Labor or prelabor membrane rupture
Pilot Study of Extracorporeal Removal of Soluble Fms-Like Tyrosine Kinase 1 in Preeclampsia

Background: Removing sFlt-1 may benefit women with very preterm (32 wks) preeclampsia

Methods:

- first showed negatively charged dextran sulfate cellulose columns adsorb sFlt-1 in vitro
- spiked 25 g of recombinant sFlt-1 protein into 2 U of discarded human whole blood
- 50 mL of human amniotic fluid, known to carry endogenous sFlt-1 isoforms

Thadani et al. Circulation. 2011
## Methods

<table>
<thead>
<tr>
<th>Experiment With DL75 (Dextran Sulfate)*</th>
<th>sFlt-1 in pg/ml</th>
<th>Reduction Ratio, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (pre)</td>
<td>4576</td>
<td></td>
</tr>
<tr>
<td>Run 1 (post)†</td>
<td>2273</td>
<td>50.3</td>
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<tr>
<td>Run 2 (post)†</td>
<td>1611</td>
<td>64.8</td>
</tr>
<tr>
<td>Run 3 (post)†</td>
<td>1185</td>
<td>74.1</td>
</tr>
</tbody>
</table>

Thadani et al. *Circulation*. 2011
In 5 women with very preterm preeclampsia (< 32 weeks) and elevated circulating sFlt-1 levels, demonstrated that a single dextran sulfate cellulose apheresis treatment reduces circulating sFlt-1 levels in a dose-dependent fashion.

Thadani et al. *Circulation*. 2011
Single dextran sulfate cellulose apheresis Rx reduces circulating sFlt-1 levels

<table>
<thead>
<tr>
<th>Characteristics on day of apheresis</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>22</td>
<td>26</td>
<td>37</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9</td>
<td>24.3</td>
<td>29.7</td>
<td>21.8</td>
<td>31.8</td>
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<tr>
<td>Gestational age, weeks + days</td>
<td>29+0</td>
<td>31+3</td>
<td>29+0</td>
<td>24+6</td>
<td>28+3</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>186</td>
<td>150</td>
<td>223</td>
<td>211</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>96</td>
<td>104</td>
<td>116</td>
<td>104</td>
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<table>
<thead>
<tr>
<th>Laboratory tests on day of apheresis</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin, g/L</td>
<td>13.2</td>
<td>12.3</td>
<td>12.0</td>
<td>11.1</td>
<td>10.7</td>
</tr>
<tr>
<td>Platelets, ×10⁹/L</td>
<td>276</td>
<td>199</td>
<td>172</td>
<td>203</td>
<td>237</td>
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<tr>
<td>Creatinine, μmol/L</td>
<td>61</td>
<td>53</td>
<td>57</td>
<td>52</td>
<td>37</td>
</tr>
<tr>
<td>SGOT, U/L</td>
<td>87</td>
<td>31</td>
<td>20</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>SGPT, U/L</td>
<td>64</td>
<td>24</td>
<td>18</td>
<td>39</td>
<td>25</td>
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<tr>
<td>LDH, U/L</td>
<td>265</td>
<td>185</td>
<td>232</td>
<td>186</td>
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<table>
<thead>
<tr>
<th>Pre- and post-pheresis measurements</th>
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<tbody>
<tr>
<td>sFlt-1 before, pg/ml†</td>
<td>14232</td>
<td>13628</td>
<td>12490</td>
<td>18168</td>
<td>8818</td>
</tr>
<tr>
<td>sFlt-1 after, pg/ml</td>
<td>12138</td>
<td>11249</td>
<td>10126</td>
<td>14251</td>
<td>6360</td>
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<tr>
<td>% sFlt-1 reduction</td>
<td>14.7</td>
<td>17.5</td>
<td>18.9</td>
<td>21.6</td>
<td>27.9</td>
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<tr>
<td>Urine PC ratio before</td>
<td>446</td>
<td>2983</td>
<td>2588</td>
<td>1168</td>
<td>6583</td>
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<tr>
<td>Urine PC ratio after (nadir)</td>
<td>—</td>
<td>1250</td>
<td>1026</td>
<td>618</td>
<td>2500</td>
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<tr>
<td>Fibrinogen before, g/L</td>
<td>3.5</td>
<td>4.0</td>
<td>3.6</td>
<td>2.0</td>
<td>3.6</td>
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<tr>
<td>Fibrinogen after, g/L</td>
<td>—</td>
<td>3.7</td>
<td>—</td>
<td>1.4</td>
<td>3.0</td>
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<tr>
<td>Volume treated, mL</td>
<td>1916</td>
<td>2500</td>
<td>5900</td>
<td>5459</td>
<td>4300</td>
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<tr>
<td>Apheresis duration, min</td>
<td>60</td>
<td>108</td>
<td>105</td>
<td>134</td>
<td>120</td>
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<tr>
<td>Duration of pregnancy after apheresis, d</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Reason for delivery†</td>
<td>Worsening</td>
<td>Worsening</td>
<td>HELLP</td>
<td>HELLP</td>
<td>Worsening of pre-eclampsia syndrome and evidence of slowing fetal heart rate</td>
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</tbody>
</table>

*Table 4. Characteristics of 5 Women With Very Preterm Preeclampsia Who Underwent a Single Extracorporeal Apheresis Treatment*
# Apheresis Treatments to Prolong Pregnancy

Table 5. Characteristics of 3 Patients With Very Preterm Preeclampsia Who Underwent $\geq 2$ Extracorporeal Apheresis Treatments

<table>
<thead>
<tr>
<th>Characteristics prior to pheresis</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>32</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>26.5</td>
<td>27.4</td>
<td>28.4</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>186</td>
<td>187</td>
<td>175</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>110</td>
<td>81</td>
<td>100</td>
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<th>Patient 3</th>
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<tbody>
<tr>
<td>Hemoglobin, g/L</td>
<td>12.9</td>
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<td>11.1</td>
</tr>
<tr>
<td>Platelets, $\times 10^9$/L</td>
<td>234</td>
<td>222</td>
<td>244</td>
</tr>
<tr>
<td>Creatinine, $\mu$mol/L</td>
<td>67</td>
<td>41</td>
<td>57</td>
</tr>
<tr>
<td>SGOT, U/L</td>
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<td>53</td>
<td>64</td>
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<tr>
<td>SGPT, U/L</td>
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<tr>
<td>LDH, U/L</td>
<td>247</td>
<td>195</td>
<td>263</td>
</tr>
</tbody>
</table>

Thadani et al. *Circulation*. 2011
## Apheresis Treatments to Prolong Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th>PATIENT 2</th>
<th>PATIENT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gest Age (wks)</td>
<td>28+3</td>
<td>30+0</td>
<td>27+5</td>
</tr>
<tr>
<td>No of apheresis Rx</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>% reduction of sflt1</td>
<td>30/34</td>
<td>26/34</td>
<td>-/-/23/25</td>
</tr>
<tr>
<td>Weeks at delivery</td>
<td>30 + 0</td>
<td>32 + 5</td>
<td>30 + 6</td>
</tr>
<tr>
<td>Reason for delivery</td>
<td>Headaches, elevated BP</td>
<td>Spontaneous ROM</td>
<td>Onset of labor (C section)</td>
</tr>
<tr>
<td>Newborn</td>
<td>55 days in NICU, minimal monitoring At 4 weeks, normal milestones</td>
<td>Twins, CPAP, no vent support At 5 weeks follow up, normal milestones</td>
<td>NICU with CPAP X5 days, regular neonatal bed x 4 weeks Normal at DC</td>
</tr>
</tbody>
</table>

Adapted from Thadani et al. *Circulation*. 2011
Conclusion

This pilot study supports the hypothesis that extracorporeal apheresis can lower circulating sFlt-1 in very preterm preeclampsia.

Further studies are warranted to determine whether this intervention safely and effectively prolongs pregnancy and improves maternal and fetal outcomes in this setting.

Thadani et al. Circulation. 2011
Long term sequelae

Systematic review and meta-analysis: women with pre-eclampsia are more likely to develop long-term sequelae
- chronic hypertension (OR 3.13)
- cardiovascular disease (OR 2.28)
- stroke (OR 1.76), diabetes (OR 1.80)
- ESRD (RR 4.70)

ESRD increase progressively with the number of pregnancies affected by pre-eclampsia

Women with pre-eclampsia are more likely to have microalbuminuria 3–5 years after delivery than women with a normal pregnancy

Nat Reviews Sept 2014
Thank You

Aim: Explore the degree and nature of glom dysfunction in PET

Methods:
- Physiologic techniques used to estimate GFR, RPF and afferent oncotic pressure
- PET (N=13) vs healthy pregnant controls (N=12)
- Morphometric analysis of biopsied glomeruli and mathematical modeling used to estimate Kf
- Glomeruli from healthy female kidney transplant donors served as structural controls (N = 8)

Results:
- GFR in PET vs controls: 91 +/- 23 vs 149 +/- 34 ml/min/1.73 m2 (P < 0.0001)
- RPF and oncotic pressure similar in the two groups (P = NS)
- Reduction in the density and size of endothelial fenestrae and subendothelial accumulation of fibrinoid deposits in PET vs controls, 1.81 versus 2.58 x 10(-9) m/sec/PA.
- Mesangial cell interposition also curtailed effective filtration surface area
- These changes lowered the computed single nephron Kf in PET below control, 4.26 vs 6.78 nl/min x mm Hg

Conclusion: The proportionate (~40%) depression of Kf for single nephrons and GFR suggests that hypofiltration in PET does not have a hemodynamic basis, but is a consequence of structural changes that lead to impairment of intrinsic glomerular ultrafiltration capacity
Evaluated anti-VEGF neutralizing antibodies and sFlt-1 in the induction of proteinuria

Took CD1 mice and injected them with a single injection of anti-VEGF antibody or sFlt-1/Fc at 3.25

Collected urine at 0, 1, 3, 5, and 24 hours after the initial injection

Sacrificed mice and stained kidneys with antibodies to nephrin, podocin, CD-2Ap or alpha actinin 4

Demonstrated anti-VEGF Abs and sFlt-1 cause rapid glomerular endothelial cell detachment and hypertrophy and down-regulation of nephrin