A Model of Pre-eclampsia in Rats: The Reduced Uterine Perfusion Pressure (RUPP) Model

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Running Head: Rat Model of Pre-eclampsia

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Abstract

Pre-eclampsia is defined as new onset hypertension with proteinuria after 20 weeks gestation and is hypothesized to be due to shallow trophoblast invasion into the spiral arteries thus resulting in progressive placental ischemia as the fetus grows. Many animal models have been developed that mimic changes in maternal circulation or immune function associated with preeclampsia. The model of reduced uterine perfusion pressure (RUPP) in pregnant rats closely mimics the hypertension, immune system abnormalities, systemic and renal vasoconstriction, and oxidative stress in the mother, and intrauterine growth restriction found in the offspring. The model has been successfully used in many species; however, rat and primate are the most consistent in comparison of characteristics with human preeclampsia. The model suffers, however, from lack of the ability to study the mechanisms responsible for abnormal placentation that ultimately leads to placental ischemia. Despite this limitation, the model is excellent for studying the consequences of reduced uterine blood flow as it mimics many of the salient features of preeclampsia during the last weeks of gestation in humans. This review discusses these features.

Key words: pregnancy, sFlt-1, AT1 receptor autoantibodies, endothelin, angiotensin II, immune system, TNFα.
Preeclampsia is a multisystem disorder that typically occurs during the second half of pregnancy and complicates approximately 3-7% for nulliparous and 1-3% for multiparous pregnancies (96). It is a major cause of maternal morbidity and mortality, prenatal death and intrauterine growth restriction (IUGR), and contributes to ~15% of all preterm pregnancies (73, 96). Preeclampsia is characterized by new onset (pregnancy-specific) maternal hypertension, proteinuria, widespread maternal endothelial dysfunction, an imbalance of angiogenic factors and typically occur after 20 weeks gestation (72). Although the mechanism(s) responsible for preeclampsia are unclear, hypertension associated with preeclampsia remits after delivery, implicating the placenta as the culprit in the disease progression. In support of this notion, Magann and colleagues reported that curettage immediately following delivery was more efficacious in the resolution of the hypertension in severely hypertensive women with preeclampsia than antihypertensive treatment with nifedipine (67).

Pre-eclampsia is associated with abnormal uteroplacental blood flow: It has been hypothesized that preeclampsia arises from reductions in uteroplacental perfusion, leading to fetoplacental ischemia (82,83). The mechanisms leading to reduced placental perfusion in preeclampsia are not clear, but studies in humans implicate impaired first trimester cytotrophoblast invasion of spiral arterioles as an important factor. During weeks 8 to 18 of normal pregnancy, the villous cytotrophoblasts originating from the fetus invade the uterine wall through the entire depth of the endometrium and the inner third of the myometrium (42,82) (see Figure 1). As a result, the spiral arteries are extensively remodeled replacing their smooth muscle and endothelium by the invading cytotrophoblasts. These arteries become widely dilated, with low resistance, and are less responsive, or even refractory, to vasoconstrictor substances (45). This normal invasive vascular remodeling occurring early in placentation, is abnormal in pregnant women that develop preeclampsia (45). Thus pre-eclampsia is thought to be caused by a reduction in uterine blood flow due to abnormal trophoblast invasion of the spiral
arteries, a concept first suggested by Young in 1914 (107). In support of this hypothesis, pre-eclamptic human placental bed biopsies indicate shallow trophoblast invasion, as compared with normal pregnancy. As a result, the corresponding arterial segments remain undilated, leading to insufficient blood flow to the uteroplacental unit and the maternal circulation remains responsive to vasoconstrictors, such as angiotensin II (Ang II) (18), and endothelin (ET-1) (51). The ischemic placenta releases cytokines, reactive oxygen species, and anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) (35), soluble endoglin (69,70), and Ang II type 1 receptor autoantibodies (AT1-AA) (100), into the circulation, making this an aggravated interaction between maternal and fetal circulation. It should be mentioned that studies in double knockout Rag2(-/-)Il2rg(-/-) mice in which there is no spiral artery remodeling during pregnancy, placental ischemia is present, but this does not result in IUGR or hypertension (25). These data suggest that other mechanisms are involved in the development of pre-eclampsia in addition to poor spiral artery remodeling at least in the mouse.

Animal models for the study of pre-eclampsia:

An ideal animal model to study preeclampsia should duplicate the pathogenesis of preeclampsia in women, including failure of early immune mechanisms, impaired first trimester trophoblast invasion and placentation, reduced uteroplacental perfusion, fetoplacental ischemia, thus resulting in systemic inflammation, proteinuria and endothelial dysfunction in the mother and restricted growth in the fetus. However, preeclampsia is thought to occur spontaneously only in women, and only very few cases reported in great apes, including chimpanzees (49,91) and gorillas (15,95). The use of non-human primates and other animal species as models for pre-eclampsia are discussed at length in a review by Podjarny et al. (80), and McCarthy et al. (72).
There is evidence that hypertensive inbred BPH-5 mice, derived from brother-sister mating of borderline hypertensive BPH/2 mice, exhibit further increases in blood pressure in late gestation (from approximately 130 mm Hg to 160 mm Hg, compared to approximately 105 mm Hg in control C57BL-6), that resolves within two days of delivery, and is accompanied by increases in proteinuria and IUGR of the pups (26,28). The mechanisms responsible for the increased blood pressure during pregnancy in this model have not been elucidated, but adenoviral vector mediated-VEGF121 (46) and tempol (103) prevented the increase in blood pressure (Woods), suggesting that placental ischemia and oxidative stress may contribute to the further elevated blood pressure.

Models to evaluate a single pathway in the progression of pre-eclampsia  There are several genetically-manipulated mouse models of preeclampsia that affect a single gene, such as sFlt-1, the renin-angiotensin system, VEGF, endothelin, endothelial nitric oxide synthase, etc. (47). These models have varying levels of similarity with human pre-eclampsia, although, interestingly, few develop new onset hypertension close to term. Readers are referred to a recent review by Ishida and colleagues for more information on mouse models of pre-eclampsia (47). Below we discuss studies performed in models other than mice to learn more about the role of specific pathways hypothesized to contribute to the pathogenesis of pre-eclampsia.

Nitric oxide inhibition. Nitric oxide (NO) is an important mediator in controlling vascular tone, endothelial function and oxidative stress. Increased NO production plays a critical role in the maternal BP and glomerular hemodynamic adaptation to pregnancy. NO production is reduced in preeclampsia (22,27). Chronic NO synthase (NOS) inhibition in pregnant rats causes a dose dependent increase in BP, renal vasoconstriction, proteinuria, maternal morbidity, and mortality and intrauterine growth restriction of pups (19,74,106). However, plasma from women with preeclampsia increases, rather than decreases, endothelial cell NO
(16), and the effect of pregnancy on BP in endothelial NOS knockout mice is controversial, with one study reporting typical pregnancy-induced decreases in BP (89), while another reported a further increase of BP during pregnancy (43).

**Anti-angiogenic factors:** Women with preeclampsia have elevated circulating sFlt-1, a soluble vascular endothelial growth factor (VEGF) receptor binding to and inactivating VEGF and placental growth factor (PIGF), critical players in angiogenesis and placentation. Placental and amniotic sFlt-1 levels are elevated, while plasma levels of free VEGF and PIGF are decreased (70). Adenoviral vector-mediated sFlt-1 in pregnant rats resulted in increased BP, proteinuria, glomerular endotheliosis, and decreases in plasma free VEGF and PIGF (70). Similar studies performed in mice resulted in similar vascular effects with significantly lower pup and placental weight (66). In later studies performed by Murphy et al., sFlt-1 infusion in rats increased vascular/placental oxidative stress, decreased vasodilatory responses to agonists, reduced placenta and fetal weight, decreased maternal circulating VEGF and NO, and increased renal preproendothelin (Prepro-ET-1) (17,76). Importantly, the effects of sFlt-1 also occurred in a dose dependent manner in non-pregnant controls, indicating these results are not specific for pregnancy, suggesting that increases in sFlt-1 under any circumstances compromise the cardiovascular system.

**Models based on Inflammatory mediators:** Women with preeclampsia exhibit increased systemic inflammation, heightened oxidative stress, and circulating autoantibodies (AT1-AA) which bind and activate Ang II type 1 receptor (AT1R) (52,86,87,100). Pregnant mice injected with human AT1-AA developed progressive hypertension, proteinuria and glomerular endotheliosis, all of which were blocked by AT1R antagonism (108). More specific studies indicated that infusion of rat AT1-AA from day 12 to day 19 of gestation into pregnant rats resulted hypertension, elevated plasma sFlt-1, and renal and placental ET-1, and oxidative stress (54,79). However, infusion of rat AT1-AA has no vascular or tissue effects in nonpregnant
rats. These findings are interesting since they suggest that the milieu of pregnancy is necessary for AT1-AA to cause adverse cardiovascular effects.

Pre-eclamptic women also have elevated inflammatory mediators, such as tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and CD4(+) T cells (52). Pregnant rats receiving TNFα infusion from days 14 to 19 of gestation displayed hypertension, and increases in preproET-1 in placenta, aorta, and kidneys (60). Pretreatment with the ET-1 receptor A (ETA) receptor antagonist abolished the BP response to TNFα. Infusion of IL-6 into pregnant rats resulted in the development of hypertension and renal vasoconstriction without affecting ET-1 levels (20). Interestingly, later studies demonstrated that infusion of TNFα or IL-6 stimulated AT1-AAs and the resulting hypertension was completely abolished by AT1R blockade (56,100). Importantly, CD4+ T helper cells, shown to be elevated in pre-eclamptic women and in RUPP rats, cause hypertension when transferred from RUPP into normal pregnant rats (99). It is important to emphasize that none of these factors, elevated TNFα, IL-6, CD4+ T cells, or AT1-AA, cause hypertension in nonpregnant rats, indicating the importance of inflammatory mediators in the progression of hypertension in response to placental ischemia and preeclampsia.

The Reduced Uterine Perfusion Pressure (RUPP) Model: Since pre-eclampsia is thought to be caused by a reduction in uterine blood flow due to abnormal trophoblast invasion of the spiral arteries, the development of a model that exploits this reduction in uterine perfusion pressure and flow is a natural alternative for study. RUPP models have been performed in dogs (104,105), rabbits (3,65), sheep (23,61), guinea pigs (39), primates (4,20) (see Table 1), and rats (1,11,29). It should be noted that differences in placentation between animal models (e.g. sheep) and humans may alter the cardiovascular responses to the RUPP maneuvers. Furthermore, in sheep, increased blood pressure only occurs with RUPP when dams are given high salt diet (61). The most well-characterized and utilized is the RUPP pregnant rat model (see Table 3). To our knowledge there have been no studies using the RUPP model in mice.
Method to induce the RUPP model in pregnant rats: The RUPP rat model of preeclampsia was adapted by Granger and colleagues, and the clipping procedure is tightly controlled, in terms of gestation time and silver clip position and size (24). Pregnant rats weighing approximately 200-250g undergo clipping at day 14 of gestation, in which a silver clip (0.203 mm ID) is placed around the aorta above the iliac bifurcation (see Figure 2). Since compensatory blood flow to the placenta occurs via adaptive increase in ovarian blood flow, both right and left uterine arcades are also clipped (silver clip, 0.100 mm ID) (11). These procedures reduce uterine blood flow in the gravid rat by approximately 40% (24).

Characteristics of the RUPP model: The RUPP rat mimics numerous physiological features of preeclampsia in women (see Table 2), including hypertension (~20-30 mmHg increase in mean arterial pressure), proteinuria (~5-fold increase in urinary protein excretion), impaired renal function, as indicated by reduction in GFR (<40%) and renal plasma flow (<23%), an increase in vascular reactivity, a reduction in cardiac index (90), and increases in leptin (14) and blood lactate (36). Fetal intrauterine growth restriction (IUGR) also occurs in RUPP rats, with decreased litter size and pup weight (10,40).

RUPP rats have reductions in NO (24) and increases in vasoconstrictor substances or response (84). Vascular smooth muscle cells isolated from renal interlobular arteries displayed increased contractility to Ang II via enhanced calcium entry (75). Inhibition of Ang II synthesis with a converting-enzyme inhibitor had no effect on the BP in RUPP rats (8), but in contrast, treatment of RUPP rats with losartan, the AT1R antagonist, significantly reduced their BP (58). These findings lead to the discovery that, just as in women with pre-eclampsia, RUPP rats have increased AT1-AA which causes activation of AT1R and is a contributor to hypertension in the model (100). RUPP rats also exhibit increased tissue ET-1, and ET_{A}R antagonists attenuate the BP increases (93). Furthermore, as in women with preeclampsia, sera from RUPP rats causes
endothelial cell activation which is attenuated by AT1R blockade, suggesting a role for the AT1-AA in the circulation of RUPP rats to activate the AT1R on the vascular endothelium (84).

As discussed previously, women with pre-eclampsia have increases in the levels of inflammatory cytokines (52). In RUPP rats, serum levels of TNFα and IL-6 are increased, and infusion of TNFα or IL-6 increases BP in normal pregnant rats, suggesting that inflammation could contribute to the hypertension of RUPP rats (30,59). Supporting this notion, administration of a TNFα soluble receptor, etanercept, attenuated the hypertension, reduced ET-1 transcript expression, and endothelial cell activation from RUPP rats (55). Sunderland and colleagues recently reported similar findings with infusion of TNFα into pregnant baboons, that also resulted in increases in sFLT-1 and soluble endoglin (92).

Angiostatic factors, such as sFlt-1 and soluble endoglin, may be important in development and progression of preeclampsia in women (69,98). RUPP rats exhibit increased plasma and placental sFlt-1, and decreased plasma VEGF and PIGF (35). A recent study demonstrated that chronic infusion of recombinant VEGF-121 during late gestation restored GFR and endothelial function and reduced BP in RUPP rats (38). Serum and placental soluble endoglin are increased along with placental hypoxia-inducible factor-1α (HIF-1α) expression, whereas placental heme oxygenase-1 (HO-1) is decreased in the RUPP rats (37). An HO-1 inducer attenuates the increases in BP, placental superoxide, placental sFlt-1/VEGF ratios and preproET-1 mRNA in RUPP rats (33). Oxidative stress, as measured by 8-isoprostane and malondialdehyde, is also increased, and renal superoxide dismutase activity is decreased in RUPP rats. Chronic treatment with tempol attenuates the hypertension associated with RUPP (88). George and colleagues have recently shown that the reduction in sFlt-1 with heme oxygenase induction is mediated via production of antioxidants, biliverdin and carbon monoxide (32,34).
Advantages of the RUPP model: The RUPP model of preeclampsia resembles numerous features exhibited by women with preeclampsia (Table 2), and serves as a good tool for investigating potential mechanisms underlying hypertension induced by placental ischemia in pregnancy. Importantly, RUPP models also successfully develop fetal IUGR, which is not always seen in other animal models of preeclampsia, and is a very useful model for studying fetal programming of cardiovascular disease. The RUPP model has also been exploited in non-human primates by Macris and colleagues, who find similar changes such as hypertension and elevated sFlt-1 (68). The RUPP model provides the opportunity to study potential therapeutic approaches for management of preeclampsia that may not be appropriate for study in women due to the consideration of the health of the fetus.

Limitations of the RUPP model: Despite the utility of the RUPP model of preeclampsia, the model does have several limitations. First, an increase in BP with RUPP does not always occur in all species or even within the same species (5). The RUPP model developed by Granger, LaMarca, Alexander and colleagues in rats requires the clipping of both the lower abdominal aorta and the uterine arteries on day 14 of gestation in approximately 250 g female rats (78). Thus the conditions to produce the model must be rigorous to have a successful outcome of hypertension that recedes after delivery of the pups. The use of rats as a RUPP model is cost effective, but somewhat limited since the clipping is performed at day 14 of gestation which only lasts 21-22 days. Thus the window for study is narrow in the rat. The use of non-primates for the RUPP model, as characterized by Hennessy and colleagues (68), provides a longer gestation time, placentation and trophoblast invasion closer to humans than rats, but is significantly more costly to maintain the animals.

A second important limitation of the RUPP model is that it only mimics the pathogenesis responsible for the hypertension in preeclampsia down stream of mid-gestational placental ischemia. Thus the RUPP model is not useful to investigate the early immune mechanisms,
trophoblast invasion, and vascular remodeling abnormalities. Furthermore, aortic clipping may have an hemodynamic impact on sympathetic nervous system and cardiac output, since Granger and colleagues reported that the RUPP procedure results in reductions in blood flow to the heart, stomach, intestine and skeletal muscle, without differences in blood flow to the brain, liver, kidney, or spleen when compared with the normal pregnant rats (90).

A third limitation is that the RUPP model in the rat does not mimic the glomerular endotheliosis that is one of the hallmarks of preeclampsia (62). This may be important because several investigators find that podocyte shedding occurs in women with preeclampsia and may be an early marker for preeclampsia (6,31).

Finally, the RUPP model is not successful in mimicking severe preeclampsia, which is characterized by the HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome. RUPP rats do not have changes in hemoglobin, platelets, liver function (48).

Summary: In conclusion, pregnancy in women involves unique fetal villous trophoblast invasion and placental vascular remodeling, namely placentation. This process is only seen in women and great apes. Thus to our knowledge, preeclampsia occurs spontaneously only in women and great apes due to abnormal placentation and the resulting placental ischemia. Thus, to our knowledge no animal model of preeclampsia can mimic the entire pathogenesis of the disease as seen in women. A variety of animal models, including genetically manipulated mouse models, have been developed based on a single mediator of preeclampsia, that only reflect limited aspects of the mechanisms underlying the disease; however, these are useful to identify mechanisms that could potentially contribute to the pathogenesis of pre-eclampsia. The RUPP model has been performed in various species (see Table 1) and involves induction of placental ischemia by reducing uterine blood flow by some maneuver, such as placement of clips on the uterine arteries and abdominal aorta, that results in a pre-eclamptic state. The RUPP model in the rat has been the most extensively studies (see Table 3) and exhibits many
of the manifestations of preeclampsia (see Table 2). Unfortunately, the greatest limitation of the RUPP model is its lack of suitability for the study of early placentation and the subsequent pathogenesis responsible for placental ischemia, such as early occurring abnormal immune mechanisms or trophoblast invasion and vascular remodeling. However, the RUPP model is excellent for the study of many of the consequences of placental ischemia, including hypertension, vascular dysfunction, and immune dysfunction. The ability to develop the RUPP model in both rats and non-human primates makes it advantageous for many future studies. Whether the RUPP model could be developed in mice is not clear.

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**Figure and table legends**

**Figure 1. The three-stage model of preeclampsia.** Stages 1 and 2 of pre-eclampsia are well accepted, whereas stage 0 is hypothetical. Based on this model, pre-eclampsia is proposed to arise from abnormal maternal immune response to feto-paternal antigens in the early stage of pregnancy (stage 0), leading to poorly perfused placenta in stage 1, which further causes multiple stresses and the final clinical manifestations in stage 2 of pre-eclampsia (82,83).

**Figure 2. Induction of reduced uterine perfusion pressure (RUPP) model in pregnant rats.** In the rat RUPP model, laparotomy is performed through an abdominal incision on day 14 of gestation. A silver clip with a 0.203 mm internal diameter is placed around the aorta right above the iliac bifurcation, and silver clips with 0.1 mm internal diameter were placed around the left and right uterine arcade at the ovarian artery before the first segmental artery. Uterine perfusion pressure in the gravid rat is reduced by approximately 40%. BP is measured via a carotid arterial catheter.
Figure 1.

Stage 0
3-8 weeks

**Poor immunoregulation:**
inadequate maternal tolerance to feto-paternal antigens during conception and implantation

Stage 1
8-18 weeks

**Poor placentation:**
deficient of trophoblast invasion and spiral artery remodeling

Oxidative stress
Endoplasmic reticulum stress
Inflammatory stress

Stage 2
20 weeks - term

**Clinical manifestation:**
over activation of maternal endothelium and systemic inflammatory network
Figure 2.
<table>
<thead>
<tr>
<th>Species</th>
<th>Method</th>
<th>Characteristics</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Occlusion of abdominal aorta below the renal arteries</td>
<td>Inc BP, UPrV, glomerular lesions, fluid retention, diffuse hemorrhagic infarction of the placenta</td>
<td>3,5,77,104,105</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Clamp or ligation of aorta proximal to the ovarian and distal to the renal arteries</td>
<td>Inc BP, UPrV, PVR, IUGR; endothelial swelling, inc glomerular fibrinogenRVR, placental lesions</td>
<td>2,3,65</td>
</tr>
<tr>
<td>Non-human primate</td>
<td>Red. abdominal aortic blood flow below kidneys</td>
<td>Inc BP, UPrV, RVR, serum uric acid, dec PRA, endotheliosis of glomeruli, inc sFlt-1</td>
<td>4,20,68,91</td>
</tr>
<tr>
<td>Guinea</td>
<td>Banding uterine arteries, ovarian arteries</td>
<td>Inc BP, UPrV, creatinine</td>
<td>39</td>
</tr>
<tr>
<td>Sheep</td>
<td>Occluder around internal iliac artery or abdominal aorta distal</td>
<td>Inc BP only with high salt diet, IUGR</td>
<td>23,61,94</td>
</tr>
</tbody>
</table>
to renal arteries

**Abbreviations:** inc, increased; dec, decreased; BP, blood pressure; UPrV, proteinuria; PRV, peripheral vascular resistance; RVR, renal vascular resistance; PRA, plasma renal activity; sFLT-1, soluble fms-like tyrosine kinase-1; IUGR, intrauterine growth restriction.
<table>
<thead>
<tr>
<th>characteristic</th>
<th>women with pre-eclampsia</th>
<th>RUPP in rats</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>new onset hypertension</td>
<td>yes</td>
<td>yes</td>
<td>11</td>
</tr>
<tr>
<td>abnormal placentation</td>
<td>yes</td>
<td>no</td>
<td>42, 45, 82, 83</td>
</tr>
<tr>
<td>proteinuria</td>
<td>yes</td>
<td>yes</td>
<td>11</td>
</tr>
<tr>
<td>renal plasma flow</td>
<td>dec</td>
<td>dec</td>
<td>90</td>
</tr>
<tr>
<td>GFR</td>
<td>dec</td>
<td>dec</td>
<td>11</td>
</tr>
<tr>
<td>Inflammation (TNF-α, IL-6, CD4+ T cells)</td>
<td>inc</td>
<td>inc</td>
<td>30, 59, 99</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>inc</td>
<td>inc</td>
<td>88</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>inc</td>
<td>inc</td>
<td>33</td>
</tr>
<tr>
<td>sFlt-1</td>
<td>inc</td>
<td>inc</td>
<td>35</td>
</tr>
<tr>
<td>VEGF, PIGF</td>
<td>dec</td>
<td>dec</td>
<td>35</td>
</tr>
<tr>
<td>Soluble endoglin</td>
<td>inc</td>
<td>inc</td>
<td>37</td>
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<tr>
<td>Placental HIF-1α</td>
<td>inc</td>
<td>inc</td>
<td>37</td>
</tr>
<tr>
<td>AT1-AA</td>
<td>inc</td>
<td>inc</td>
<td>58</td>
</tr>
<tr>
<td>Glomerular endotheliosis</td>
<td>yes</td>
<td>no</td>
<td>62</td>
</tr>
<tr>
<td>Podocyte shedding</td>
<td>yes</td>
<td>??</td>
<td>6, 31</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>in severe cases</td>
<td>no</td>
<td>48</td>
</tr>
<tr>
<td>Fetal IUGR</td>
<td>yes</td>
<td>yes</td>
<td>7, 52</td>
</tr>
</tbody>
</table>
**Abbreviations:** inc, increased; dec, decreased; GFR, glomerular filtration rate; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; sFlt-1, soluble fms-like tyrosine kinase-1 (VEGF receptor-1); VEGF, vascular endothelial growth factor; PIGF, placental growth factor; HIF-1α, hypoxia-inducible factor-1α; AT1-AA, agonistic autoantibodies against angiotensin Type 1 receptor; HELLP syndrome, hemolysis, elevated liver enzymes, low platelets; IUGR, intrauterine growth restriction.
Table 3: Summary of studies done in rat model of reduced uterine perfusion pressure (RUPP):

<table>
<thead>
<tr>
<th>Year</th>
<th>Methods employed</th>
<th>Results of the study</th>
<th>Ref #</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>characterization of the model</td>
<td>Inc. BP, dec GFR, RPF, nNOS</td>
<td>11</td>
</tr>
<tr>
<td>2001</td>
<td>blockade of endothelin ETA receptor</td>
<td>RUPP causes inc. preproET mRNA, Dec BP with Abt627</td>
<td>9</td>
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<tr>
<td>2001</td>
<td>blockade with CEI</td>
<td>RUPP causes Inc PRA</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enalapril has no effect on BP</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>blockade of thromboxane receptor</td>
<td>RUPP causes inc TxB2</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQ29548, no effect on BP</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>characterization of IUGR with RUPP</td>
<td>Inc BP at 4 wks, sex difference in BP at 12 wks, small for gestational age</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Catch-up growth by 12 wks</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>blockade of eicosanoid, 20-HETE</td>
<td>1-ABT dec BP, 20-HETE in renal cortex</td>
<td>63</td>
</tr>
<tr>
<td>2004</td>
<td>L-arginine infusion</td>
<td>Dec BP &gt; than in NP</td>
<td>12</td>
</tr>
<tr>
<td>2005</td>
<td>measurement of TNFα</td>
<td>RUPP inc serum TNFα</td>
<td>53</td>
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<tr>
<td>2005</td>
<td>uterine arcuate artery function</td>
<td>Inc response to vasoconstrictor, dec response to vasodilators</td>
<td>13</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
<td>Outcome</td>
<td>Reference</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>2005</td>
<td>measurement leptin, leptin receptors</td>
<td>RUPP inc. plasma leptin, inc placental leptin receptor</td>
<td>14</td>
</tr>
<tr>
<td>2005</td>
<td>treatment with N-acetylcysteine</td>
<td>N-AC dec BP, no effect on pups</td>
<td>21</td>
</tr>
<tr>
<td>2006</td>
<td>measurement of interleukin-6</td>
<td>RUPP causes 3-fold inc IL-6</td>
<td>30</td>
</tr>
<tr>
<td>2007</td>
<td>sympathetic nerve activity (SNA)</td>
<td>RUPP inc renal SNA, shifts baroreflex sensitivity</td>
<td>44</td>
</tr>
<tr>
<td>2007</td>
<td>measurement Ang (1-7), ACE2</td>
<td>RUPP dec intrarenal Ang (1-7), no change renal ACE2 activity</td>
<td>50</td>
</tr>
<tr>
<td>2007</td>
<td>measurement sFlt-1</td>
<td>RUPP inc sFlt-1</td>
<td>35</td>
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<tr>
<td>2008</td>
<td>measurement of oxidative stress</td>
<td>RUPP inc urinary F2-IsoP, MDA, dec renal SOD activity, tempol dec BP</td>
<td>88</td>
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<td>2008</td>
<td>infusion of tempol</td>
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<tr>
<td>2008</td>
<td>AT1 receptor autoantibodies (AT1-AA)</td>
<td>RUPP causes inc AT1-AA, and TNFα losartan dec BP</td>
<td>58</td>
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<tr>
<td>2008</td>
<td>blockade of TNFα</td>
<td>etanercept dec BP</td>
<td>55</td>
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<tr>
<td>2008</td>
<td>soluble endoglin</td>
<td>RUPP inc soluble endoglin</td>
<td>37</td>
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<td>2009</td>
<td>17-α-progesterone infusion</td>
<td>dec BP, TNFα, IL-6, ET-1</td>
<td>97</td>
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<td>2009</td>
<td>treatment with RUPP plasma</td>
<td>dec mesenteric vasorelaxation</td>
<td>102</td>
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<td>Year</td>
<td>Treatment/Intervention</td>
<td>Effect/Outcome</td>
<td>Reference</td>
</tr>
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<td>2010</td>
<td>infusion of VEGF121</td>
<td>dec BP, inc GFR, RPF</td>
<td>38</td>
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<td>2010</td>
<td>TNFα, AT1-AA treatment of placental explants</td>
<td>Inc sFlt-1, s-endoglin</td>
<td>79</td>
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<td>2011</td>
<td>role of B lymphocytes</td>
<td>rituximab dec BP, AT1-AA, ET-1</td>
<td>57</td>
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<td>2011</td>
<td>infusion of CD4+ cells from RUPP into NP</td>
<td>CD4+ cells in NP inc sFlt-1, TNFα</td>
<td>99</td>
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<td>2011</td>
<td>infusion of TNFα soluble receptor</td>
<td>etanercept dec cardiomegaly, fibrosis</td>
<td>41</td>
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<td>2011</td>
<td>middle cerebral artery myogenic response</td>
<td>RUPP dec myogenic response, causes brain edema</td>
<td>85</td>
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<td>2011</td>
<td>upregulate heme oxygenase 1 (HO-1) with cobalt protoporphyrin (CoPP)</td>
<td>CoPP dec placental SOD, preproET-1</td>
<td>32,34</td>
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<td>2011</td>
<td>PPAR-γ agonist +/- HO1-antagonist</td>
<td>dec placental sFlt-1/VEGF ratio</td>
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<td>2011</td>
<td>mesenteric myogenic response</td>
<td>RUPP inc mesenteric myogenic response</td>
<td>81</td>
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<tr>
<td>2012</td>
<td>COPP inc HO-1</td>
<td>CO and biliverdin dec placental explant</td>
<td>34</td>
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Note: Dec = decrease, Inc = increase, BP = blood pressure, GFR = glomerular filtration rate, RPF = renal plasma flow, sFlt-1 = soluble fms-like tyrosine kinase 1, TNFα = tumor necrosis factor α, AT1-AA = angiotensin type 1 antagonist, ET-1 = endogenous thrombin-1, NP = newborn, BNP = brain natriuretic peptide, eNOS = endothelial nitric oxide synthase, oxytocin receptor, RUPP = unilateral uterine artery ligation, HO-1 = heme oxygenase 1, CoPP = cobalt protoporphyrin, PPAR-γ = peroxisome proliferator-activated receptor-γ, HO1-antagonist = heme oxygenase 1 antagonist, COPP = cobalt protoporphyrin, CO = carbon monoxide, biliverdin dec = decarbonyl biliverdin.
2012 poly-ADP-ribose polymerase inhibition PJ34 prior to RUPP surgery, dec BP

dec mesenteric nitrotyrosine

**Abbreviations:** inc, increased; dec, decreased; BP, blood pressure; GFR, glomerular filtration rate; RPF, renal plasma flow; nNOS, neuronal nitric oxide synthase (NOS1); preproET, preproendothelin; ET-1, endothelin-1; PRA, plasma renal activity; TxB₂, thromboxane B₂; IUGR, intrauterine growth restriction; NP, normal pregnant; ACE2, angiotensin converting enzyme 2; sFLT-1, soluble fms-like tyrosine kinase-1; eNOS, endothelial NO synthase (NOS3); SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; CO, carbon monoxide.