A model of preeclampsia in rats: the reduced uterine perfusion pressure (RUPP) model

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Preeclampsia 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 8–18 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 Fig. 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 preeclampsia 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, preeclamptic human placental bed biopsies indicate shallow trophoblast invasion, 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-/-II2rg-/- 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 preeclampsia in addition to poor spiral artery remodeling at least in the mouse.

Animal Models for the Study of Preeclampsia

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, and 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 have been reported in great apes, including chimpanzees (49, 91) and gorillas (15, 95). The use of nonhuman primates and other animal species as models for preeclampsia 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 (BP) in late gestation (from ~130 to 160 mmHg, compared with ~105 mmHg in control C57BL-6) that resolves within 2 days of delivery and is accompanied by increases in proteinuria and IUGR of the pups (26, 28). The mechanisms responsible for the increased BP during pregnancy in this model have not been elucidated, but adenoviral vector-mediated vascular endothelial growth factor (VEGF) 121 (46) and tempol (103) prevented the increase in BP (103), suggesting that placental ischemia and oxidative stress may contribute to the further elevated BP.

Models to Evaluate a Single Pathway in the Progression of Preeclampsia

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 preeclampsia, although, interestingly, few develop new-onset hypertension close to term. Readers are referred to a recent review by Ishida and colleagues (47) for more information on mouse models of preeclampsia. 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 preeclampsia.

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 IUGR 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 VEGF receptor binding to and inactivating VEGF and placental growth factor (PIGF), critical players in angiogenesis and placentaion. 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. (17, 76), 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). Importantly, the effects of sFlt-1 also occurred in a dose-dependent manner in nonpregnant 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 auto-inflammatory markers, increased lipid peroxidation, and increased levels of endogenous and exogenous proinflammatory mediators, such as TNF-α, IL-6, and C-reactive protein (65, 85). These inflammatory responses are associated with adverse pregnancy outcomes, including preeclampsia, IUGR, and fetal death. Anti-inflammatory therapies, such as indomethacin, dexamethasone, and hydrocortisone, have been shown to improve pregnancy outcomes in animal models of preeclampsia (85, 119). In addition, therapies targeting proinflammatory cytokines, such as TNF-α and IL-6, have been shown to reduce inflammation and improve pregnancy outcomes in animal models of preeclampsia (119).
antibodies (AT1-AA) that 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 in 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.

Preeclamptic women also have elevated inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and CD4\(^+\) T cells (52). Pregnant rats receiving TNF-α infusion from days 14 to 19 of gestation displayed hypertension and increases in prepro-ET-1 in placenta, aorta, and kidneys (60). Pretreatment with the ET-1 receptor A (ET\(_A\)) antagonist abolished the BP response to TNF-α. Infusion of IL-6 in pregnant rats resulted in the development of hypertension and renal vasoconstriction without affecting ET-1 levels (20). Interestingly, later studies demonstrated that infusion of TNF-α 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 preeclamptic women and in reduced uterine perfusion pressure (RUPP) rats, cause hypertension when transferred from RUPP into normal pregnant rats (99). It is important to emphasize that none of these factors, elevated TNF-α, IL-6, CD4\(^+\) T cells, or AT1-AA, causes hypertension in nonpregnant rats, indicating the importance of inflammatory mediators in the progression of hypertension in response to placental ischemia and preeclampsia.

The RUPP Model

Because preeclampsia 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 animals (e.g., sheep) and humans may alter the cardiovascular responses to the RUPP maneuvers. Furthermore, in sheep, increased BP only occurs with RUPP when dams are given a high-salt diet (61). The most well-characterized and utilized is the RUPP pregnant rat model (see Table 2). 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 Crews and colleagues (24), and the clipping procedure is tightly controlled, in terms of gestation time and silver clip position and size. Pregnant rats weighing ~200–250 g 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 Fig. 2). Because compensatory blood flow to the placenta occurs via an 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 ~40% (24).

Characteristics of the RUPP Model

The RUPP rat model of preeclampsia mimics numerous physiological features of preeclampsia in women (see Table 3), 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 glomerular filtration rate (GFR) (<40%) and renal plasma flow (<23%), increase in vascular reactivity, a reduction in cardiac index (90), and increases in leptin (14) and blood lactate (36). Fetal 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 had significantly reduced their BP (58). These findings lead to the discovery that, just as in women with preeclampsia, RUPP rats have increased AT1-AA that causes activation of AT1R and is a contributor to hypertension in the model (100). RUPP rats also exhibit increased tissue ET-1, and ET\(_A\) receptor antagonists attenuate the BP increases (93). Furthermore, as in women with preeclampsia, sera from RUPP rats causes endothelial cell activation that is attenuated by AT1R blockade.

Table 1. Models of reduced uterine perfusion pressure in animals other than rat

<table>
<thead>
<tr>
<th>Species</th>
<th>Method</th>
<th>Characteristics</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Occlusion of abdominal aorta below the renal arteries</td>
<td>Inc BP, UPyV, glomerular lesions, fluid retention</td>
<td>3, 5, 77, 104, 105</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Clamp or ligation of aorta proximal to the ovarian artery and distal to the renal arteries</td>
<td>Inc BP, UPyV, PVR, IUGR; endothelial swelling, inc glomerular fibrinogen RVR, placental lesions</td>
<td>2, 3, 65</td>
</tr>
<tr>
<td>Nonhuman primate</td>
<td>Red, abdominal aortic blood flow below kidneys</td>
<td>Inc BP, UPyV, RVR, serum uric acid, dec PRA, endotheliosis of glomeruli, inc sFlt-1</td>
<td>4, 20, 68, 91</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>Banding uterine arteries, ovarian arteries</td>
<td>Inc BP, UPyV, creatinine</td>
<td>39</td>
</tr>
<tr>
<td>Sheep</td>
<td>Occluder around internal iliac artery or abdominal aorta distal to renal arteries</td>
<td>Inc BP only with high-salt diet, IUGR</td>
<td>23, 61, 94</td>
</tr>
</tbody>
</table>

Inc, increased; dec, decreased; BP, blood pressure; UPyV, proteinuria; PVR, peripheral vascular resistance; RVR, renal vascular resistance; PRA, plasma renal activity; sFlt-1, soluble fms-like tyrosine kinase-1; IUGR, intrauterine growth restriction.

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suggested a role for the AT1-IA in the circulation of RUPP rats to activate the AT1R on the vascular endothelium (84). As discussed previously, women with preeclampsia have increases in the levels of inflammatory cytokines (52). In RUPP rats, serum levels of TNF-α and IL-6 are increased, and infusion of TNF-α 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 TNF-α soluble receptor, etanercept, attenuated the hypertension and reduced ET-1 transcript expression and endothelial cell activation from RUPP rats (55). Sunderland and colleagues (92) recently reported similar findings with infusion of TNF-α in pregnant baboons that also resulted in decreases in sFlt-1 and soluble endoglin.

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 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-to-VEGF ratios, and prepro-ET-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 tempro attenuates the hypertension associated with RUPP (88). George and colleagues (32, 34) have recently shown that the reduction in sFlt-1 with heme oxygenase induction is mediated via production of antioxidants, biliverdin and carbon monoxide.

**Advantages of the RUPP Model**

The RUPP model of preeclampsia resembles numerous features exhibited by women with preeclampsia (Table 3) and

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**Table 2. Summary of studies done in rat model of RUPP**

<table>
<thead>
<tr>
<th>Year</th>
<th>Methods Employed</th>
<th>Results of the Study</th>
<th>Ref. No.</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 ETα receptor</td>
<td>RUPP causes inc. prepro-ET mRNA, dec BP with Ab627</td>
<td>9</td>
</tr>
<tr>
<td>2001</td>
<td>Blockade with CEI</td>
<td>RUPP causes inc PRA</td>
<td>8</td>
</tr>
<tr>
<td>2002</td>
<td>Blockade of thromboxane receptor</td>
<td>Enalapril has no effect on BP</td>
<td>8</td>
</tr>
<tr>
<td>2003</td>
<td>Characterization of IUGR with RUPP</td>
<td>Inc BP at 4 wk, sex difference in BP at 12 wk, small for gestational age catch-up growth by 12 wk</td>
<td>7</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>Measurement of interleukin-6</td>
<td>Dec BP &gt; in NP</td>
<td>12</td>
</tr>
<tr>
<td>2005</td>
<td>Measurement of TNF-α</td>
<td>RUPP inc serum TNF-α</td>
<td>53</td>
</tr>
<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>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 threefold inc IL-6</td>
<td>30</td>
</tr>
<tr>
<td>2007</td>
<td>Sympathetic nerve activity (SNA)</td>
<td>RUPP inc renal SNA, shifted baroreflex sensitivity</td>
<td>44</td>
</tr>
<tr>
<td>2007</td>
<td>Measurement ANG-(1-7), ACE2</td>
<td>RUPP inc 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>
</tr>
<tr>
<td>2008</td>
<td>Measurement of oxidative stress infusion of tempol</td>
<td>RUPP inc urinary F2-Isop, MDA, dec renal SOD activity, tempol dec BP</td>
<td>88</td>
</tr>
<tr>
<td>2008</td>
<td>ATα receptor autoantibodies (AT1-AA)</td>
<td>RUPP causes inc AT1-AA, and TNF-α losartan dec BP</td>
<td>58</td>
</tr>
<tr>
<td>2008</td>
<td>blockade of TNF-α</td>
<td>Etanercept dec BP</td>
<td>55</td>
</tr>
<tr>
<td>2008</td>
<td>Soluble endoglin</td>
<td>RUPP inc soluble endoglin</td>
<td>37</td>
</tr>
<tr>
<td>2009</td>
<td>17α-Progesterone infusion</td>
<td>Dec BP, TNF-α, IL-6, ET-1</td>
<td>97</td>
</tr>
<tr>
<td>2009</td>
<td>Treatment with RUPP plasma</td>
<td>Dec mesenteric vasorelaxation</td>
<td>102</td>
</tr>
<tr>
<td>2010</td>
<td>Infusion of VEGF121</td>
<td>Dec BP, inc GFR, RPF</td>
<td>38</td>
</tr>
<tr>
<td>2010</td>
<td>TNF-α, AT1-AA treatment of placental explants</td>
<td>Inc sFlt-1, s-endoglin</td>
<td>79</td>
</tr>
<tr>
<td>2011</td>
<td>Role of B lymphocytes</td>
<td>Nituximab dec BP, AT1-AA, ET-1</td>
<td>57</td>
</tr>
<tr>
<td>2011</td>
<td>Infusion of CD4+ cells from RUPP into NP</td>
<td>CD4+ cells in NP inc sFlt-1, TNF-α</td>
<td>99</td>
</tr>
<tr>
<td>2011</td>
<td>Infusion of TNF-α soluble receptor</td>
<td>Etanercept dec cardiomely, fibrosis dec BNP, inc eNOS, oxytocin receptor</td>
<td>41</td>
</tr>
<tr>
<td>2011</td>
<td>Middle cerebral artery myogenic response</td>
<td>RUPP dec myogenic response, causes brain edema</td>
<td>85</td>
</tr>
<tr>
<td>2011</td>
<td>Upreregulate heme oxygenase (HO-1) with cobalt protoporphyrin (CoPP)</td>
<td>CoPP dec placental SOD, prepro-ET-1 dec placental sFlt-1-to-VEGF ratio</td>
<td>32, 34</td>
</tr>
<tr>
<td>2011</td>
<td>PPAR-γ agonist ± HO-1 antagonist</td>
<td>Rosiglitazone dec BP, prevented by Tin protophorphyrin</td>
<td>71</td>
</tr>
<tr>
<td>2011</td>
<td>Mesenteric myogenic response</td>
<td>RUPP inc mesenteric myogenic response</td>
<td>81</td>
</tr>
<tr>
<td>2012</td>
<td>CoPP inc HO-1</td>
<td>CO and biliverdin dec placental explant sFlt-1 and reactive oxygen species</td>
<td>34</td>
</tr>
<tr>
<td>2012</td>
<td>Poly-ADP-ribose polymerase inhibition</td>
<td>P334 before RUPP surgery, dec BP dec mesenteric nitrotyrosine</td>
<td>101</td>
</tr>
</tbody>
</table>

RUPP, reduced uterine perfusion pressure; GFR, glomerular filtration rate; RPF, renal plasma flow; nNOS, neuronal nitric oxide synthase; prepro-ET, preproendothelin; ET1, endothelin-1; ETα, ET1 receptor A; TxB2, thromboxane B2; NP, normal pregnant; ACE2, angiotensin converting enzyme 2; eNOS, endothelial nitric oxide synthase; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; CO, carbon monoxide.
against angiotensin type 1 receptor; HELLP syndrome, hemolysis, elevated liver enzymes, low platelets.

HELLP syndrome In severe cases

Podocyte shedding Yes 6, 31

Glomerular endotheliosis Yes No 62

AT1-AA Inc Inc 58

Fetal IUGR Yes Yes 7, 52

Placental HIF-1α/H9251

Soluble endoglin Inc Inc 37

VEGF, PIGF Dec Dec 35

sFlt-1 Inc Inc 35

Endothelin-1 Inc Inc 33

Oxidative stress Inc Inc 88

Inflammation (TNF-α, IL-6, CD4+ T cells) Inc Inc 30, 59, 99

Renal plasma flow Dec Dec 90

GFR Dec Dec 11

Proteinuria Yes Yes 11

AT1-AA Inc Inc 68

Hemoglobinemia. 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 nonhuman primates for the RUPP model, as characterized by Makris 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 downstream of midgestational 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 a hemodynamic impact on sympathetic nervous system and cardiac output, since Sholook and colleagues (90) 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 compared with the normal pregnant rats.

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, or 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

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 nonhuman primates by Makris and colleagues (68), who find similar changes such as hypertension and elevated sFlt-1. 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 (40), LaMarca (54–57), Alexander (7), and colleagues in rats requires the clipping of both the lower abdominal aorta and the uterine arteries on day 14 of gestation in ~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 nonhuman primates for the RUPP model, as characterized by Makris 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.

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Table 3. Comparison of characteristics in women with preeclampsia and the model of RUPP in the rat

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women with Preeclampsia</th>
<th>RUPP in Rats</th>
<th>Ref. No.</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>
</tr>
<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>Yes</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>

TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; 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.
great apes. Thus to our knowledge, preeclampsia occurs spontaneously only in women and great apes due to abnormal placentaion and the resulting placental ischemia. Thus 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 preeclamp-sia that only reflects limited aspects of the mechanisms underlying the disease; however, these are useful to identify mechanisms that could potentially contribute to the pathogenesis of preeclampsia. 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 preeclamptic state. The RUPP model in the rat has been the most extensively studied (see Table 2) and exhibits many of the manifestations of preeclampsia (see Table 3). Unfortunately, the greatest limitation of the RUPP model is its lack of suitability for the study of early placentaion 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 nonhuman primates makes it advantageous for many future studies. Whether the RUPP model could be developed in mice is not clear.

GRANTS

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REFERENCES


Review

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RAT MODEL OF PREECLAMPSIA


