Chronic maternal hypertension characterized by renal dysfunction is associated with reduced placental blood flow during late gestation in rabbits

Adelle M. McArdle, Claire T. Roberts, and Kate M. Denton

1Department of Physiology, Monash University, Melbourne Australia; and 2Discipline of Obstetrics and Gynaecology, University of Adelaide, Adelaide, Australia

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McArdle AM, Roberts CT, Maduwegedera D, Flower RL, and Denton KM. Chronic maternal hypertension characterized by renal dysfunction is associated with reduced placental blood flow during late gestation in rabbits. Am J Physiol Regul Integr Comp Physiol 298: R1043–R1049, 2010. First published January 20, 2010; doi:10.1152/ajpregu.00202.2009.—Maternal hypertension associated with renal disease is a common pregnancy complication. Previously, we have shown in a rabbit model of mild hypertension that offspring from hypertensive mothers have increased blood pressure as adults. In human pregnancy, hypertension has been associated with decreased utero-placental blood flow. The aim of this study was to determine placental blood flow (PBF) in mild (2-kidney–1-wrapped; 2K-1W) and moderate (2-kidney–2-wrapped; 2K-2W) rabbit models of maternal hypertension. We hypothesized that PBF would be inversely related to the severity of the hypertension. PBF and renal blood flow (RBF) were measured using microspheres on day 28 of a 32-day gestation, in normotensive (sham), 2K-1W, and 2K-2W hypertensive groups. Mean arterial pressure (MAP, -7 mmHg, P < 0.05) was increased, and RBF (~35%, P < 0.05) was reduced in the 2K-1W and 2K-2W (MAP ~20 mmHg, P < 0.01; RBF ~53%, P < 0.05) groups compared with the sham group. In the 2K-1W group, PBF fell by ~12% (P = 0.08) and fetal-to-placental weight ratio increased by ~12% (P < 0.01) compared with the sham group, reflecting an increase in the functional capacity of the placenta to deliver nutrients to the fetus. In the 2K-2W group, PBF decreased ~51% (P < 0.05) compared with the sham group, without changes in placental efficiency. Thus, in late gestation, placental blood flow was significantly reduced in the moderate hypertension group, without accompanying changes in fetal or placental weight or placental efficiency. In contrast, mild hypertension resulted in an increase in placental efficiency, without significant changes in placental blood flow. These findings suggest that mild and moderate hypertension may alter placental delivery of nutrients via differing mechanisms dependent upon the severity of the hypertension.

placental blood flow; rabbit; hypertension; renal blood flow

ADEQUATE UTERINE BLOOD FLOW throughout pregnancy is vital for placental and fetal growth (29). Hypertension, including maternal chronic hypertension, preeclampsia, superimposed preeclampsia, and pregnancy-induced hypertension, is a common complication during pregnancy that affects between 5 and 10% of pregnancies (42). In humans, Doppler waveforms displaying absent or reversed end-diastolic flow in the utero-umbilical-placental circulations have been shown to occur in pregnancies complicated by severe maternal hypertension, gestational hypertension, and preeclampsia (9, 28, 35, 49, 51, 52). Pregnancies characterized by these abnormal Doppler waveforms are often associated with small-for-gestational age babies. Pregnancies presenting with absent or reversed end-diastolic flow also display alterations in the placental vasculature, suggesting an association between utero-placental flow and placental vascular remodeling (45, 53). Current clinical opinion considers mothers presenting with mild-to-moderate hypertension to have obstetric outcomes not significantly different from those of the normal population (48). However, information regarding the long-term outcomes of pregnancies complicated by mild-to-moderate maternal hypertension is sparse (48).

Recently, epidemiological and experimental studies have demonstrated that cardiovascular disease can be programmed in utero by adverse conditions (3, 30, 41), and reduced uterine blood flow has been implicated as a mechanism in intrauterine programming of adult diseases (22, 44). This raises the question as to whether mild-to-moderate hypertension during pregnancy adversely affects the development of the offspring and increases the risk of adult disease. Previously, we have shown that chronic secondary renin-dependent hypertension (2 kidney-1 cellphane wrap hypertension; 2K-1W) in rabbit mothers does cause elevated arterial pressure in adult offspring (16, 32). In this model, the elevation in maternal plasma renin activity (PRA) may also alter utero-placental blood flow, as the renin angiotensin system plays an important role in placental development (25, 37, 38) and in the local control of utero-placental blood flow (2). Indeed, we have recently demonstrated that elevated maternal MAP and PRA, in a renin-dependent and a renin-independent model of hypertension differentially altered placental structural differentiation and disturbed the relationships between the placental renin-angiotensin system gene expression and placental structure (34). The rabbit offers several advantages as a model for chronic hypertension during pregnancy, not the least of which is its size. In the context of the present study the rabbit, like humans, has a mono-hemodichorial discoid placenta. That is, each fetus has its own individual placenta with a single trophoblast layer separating maternal and fetal blood (20, 33).

The aim of this study was to determine whether, in these models of chronic maternal hypertension, as in human hypertensive pregnancies (35, 52), utero-placental blood flow was reduced. If utero-placental blood flow is decreased in our rabbit models of maternal secondary hypertension that has previously been shown to program increases in blood pressure in the adult offspring (16), it would suggest that the decreases in utero-placental blood flow that are associated with human hypertensive pregnancies may also contribute to the programming of increased arterial pressure in humans. We hypothesized that chronic maternal hypertension during pregnancy would be associated with reduced utero-placental blood flow and that the reduction in placental blood flow would be proportional to the
severity of the hypertension and the degree of activation of the 
renin-angiotensin system in the mother. To test this hypothesis, 
uteroplacental blood flow was quantified during late gestation 
in two variants of the Page (cellophane wrap) model of hyper-
tension, which give pregnancies with graded severity of hyper-
tension and activation of the renin-angiotensin system. (16, 32).

METHODS

Animals. Nulliparous female English cross-bred rabbits (13 ± 1 wk 
of age, 2.61 ± 0.07 kg) were housed individually with temperature 
maintained between 20 and 22°C and a 12:12-h light-dark cycle. 
Nonpregnant rabbits were meal fed 100 g of a high-fiber low-starch 
rabbit pellets each day (Glen Forrest Stockfeeders Glen Forests, 
Western Australia, Australia), and water was provided ad libitum, 
whereas during pregnancy, food was provided ad libitum. All exper-
iments were conducted in accordance with the Australian Code of 
Practice for the Care and Use of Animals for Scientific Purposes and 
were approved by the Monash University Animal Ethics Committee. 
Surgery and experimental design. Experiments were performed in 
three groups of rabbits: 1) a control group of sham-operated animals 
(n = 8; sham), 2) a 2-kidney-1-wrapped hypertensive group (n = 10; 
2K-1W), and 3) a 2-kidney-2-wrapped hypertensive group (n = 7; 
2K-2W). Surgery to induce hypertension was performed as previously 
described (16, 32). In brief, anesthesia was induced with propofol (10 
mg/kg iv Diprivan; Sandoz, North Ryde, NSW, Australia) and 
maintained with isoflurane (Baxter Healthcare, Toongabbie, NSW, 
Australia). In the 2K-2W group, both kidneys were exposed and wrapped 
in cellophane; in the 2K-1W group, only the left kidney was wrapped 
in cellophane, and in the sham group, both kidneys were untouched. 
Four weeks were allowed for the hypertension to develop, and then 
the rabbits were mated with a normotensive male, and this was 
designated as gestational age (GA) 0 days.

Maternal measurements. Maternal body weight, mean arterial pres-
sure (MAP), and PRA were measured in conscious rabbits prior to 
surgery (control), 4-wk later at GA0 just before mating, and at GA28 
term (32 days). A catheter was placed in the central ear artery under 
local anesthetic (Xylocaine, 1% vol/vol lignocaine hydrochloride; 
Astra Pharmaceuticals, NSW, Australia), and conscious arterial pres-
sure was measured for 30 min (16). A 3-ml arterial blood sample 
was collected for measurement of PRA by radioimmunoassay (ProSearch 
International Australia, VIC, Australia) (12).

Catheter surgery. On GA28, after MAP and PRA measurements in 
conscious animals, a catheter was inserted into the left ventricle via 
the jugular vein, and a second catheter was inserted into the femoral 
artery in preparation for injection of microspheres, under the short 
acting anesthetic propofol (10 mg/kg iv Diprivan; Sandoz, NSW, 
Australia). The animal was given an analgesic (0.1 mg/kg im of 
temgesic, buprenorphine hydrochloride; Reckitt Benckiser Health-
care, Hull, UK) before cessation of the anesthetic. Recovery was seen 
within 3–5 min of the cessation of anesthetic, and the animal was 
returned to the holding box, where its recovery was continuously 
monitored for ~1 h.

Injection of microspheres. Uterine, placental, and renal blood flow 
was measured by injection of 15-μm orange microspheres, (E-Z Trac, 
Interactive Medical Technologies, Irvine, CA). Approximately 
2,000,000 microspheres, suspended in 2 ml of 0.01% Tween 80 in 
heparinized saline, were injected into the left ventricle over a period 
of 30 s. A reference blood sample was simultaneously withdrawn 
from the femoral artery catheter at a rate of 2 ml/min with a Harvard 
infusion pump, (Haddland Photonics, Victoria, Australia). Collection 
of the reference sample continued for ~2 min after the microsphere 
injection was completed. The animal was then immediately killed by 
an anesthetic overdose (pentobarbital sodium; 325 mg/kg iv; Virbac, 
NSW, Australia).

Collection of tissue. A midline incision was made, and the uterus 
was exposed. Total number and location of fetuses in each uterine 
horn were recorded. The left and right uterine horns, each individual 
placenta, and the decapsulated maternal kidneys were weighed. Pla-
cental tissue, reference blood samples, maternal kidneys, and uterine 
horns were frozen at −20°C for later determination of blood flow.

Digestion of tissue. Tissue was thawed. Whole placental tissue 
was digested in 4 ml of 2 M NaOH, while whole uterus and kidney tissue 
were digested in 15 ml 2 M NaOH, in a water bath maintained at 
90–95°C. Each sample was vigorously mixed every 15 min until all 
large aggregates of tissue were homogenized in suspension. The 
solution was then centrifuged for 30 min to allow the microspheres to 
form a pellet at the base of the tube; the remaining solution was 
decanted. Microspheres were washed with a solution of 1% EtOH, 0.05% Triton X, 0.1% Tween 80, and 0.02% sodium azide in distilled 
water. Microspheres were suspended in a known volume of solution 
containing 0.2% Tween 80, 0.02% sodium azide, and 0.1% sodium 
dodecyl benzene sulfonate in distilled water. Digestion of the refer-
ence blood sample occurred by combining the sample with a hemo-
lysis reagent (20% sodium azide, 0.2% ethanol in distilled water) until 
the combined volume reached 50 ml. The sample was centrifuged for 
30 min, and the supernatant was removed. The pellet was resuspended 
in 5 ml of 2 M NaOH and heated in a water bath, accompanied by 
vigorous mixing every 15 min until the majority of each sample was 
homogenized. The reference sample solution was subjected to the 
same process of washing and resuspension, as for the other tissue 
samples. All samples were stored at 4°C until microsphere counting 
was conducted.

Microsphere analysis. Prior to counting, each sample was centri-
fuged for 15 min to deposit any sediment that may contain micro-
spheres at the base of the tube. The total volume in the tube (micro-
spheres plus microsphere counting reagents) was adjusted until the 
solution volume was 0.5 ml. The sample was vortex mixed for 15 s to 
sure homogeneous suspension of microspheres in the counting 
reagent.

Microsphere counting was performed using an improved Bright 
line Neubauer ruling hemocytometer 1/10 mm. (Boeco, Germany), 
under ×10 magnification (Kyowa Unilux 2 light microscope). Eight-
teen-microliter aliquots of microsphere suspension were used to fill 
the chamber. The number of fields counted was determined to be 
sufficient when the cumulative mean for the number of microspheres/ 
chamber did not vary with the addition of further counts/chamber. For 
reference blood samples, 12 chambers were counted; for each pla-
centa, 10 chambers were counted; for the left and right uterine horns, 
10 chambers were counted; and for the maternal left and right kidneys, 
4 chambers were counted. The coefficient of variation was found to be 
between ~10 and 15%.

Microsphere determination of tissue blood flow. To calculate blood 
flow in the tissues, the number of microspheres in the reference 
blood sample was calculated as an estimate of the number of micro-
spheres entering the circulation, using the formula

\[ C_m = \frac{(N \times 1000 \text{ mm}^3 \times V_o) / V_C}{C_r} \]

where \( C_m \) is the total number of microspheres in the 
reference blood sample; \( N \) is total number of microsphere counted; 
\( V_C \) is the volume of suspension; and \( V_C \) is the total number of microspheres per gram 
of tissue. The total blood flow per gram of tissue was then determined 
using the formula:

\[ Q_m = \frac{C_m \times Q_r}{C_r} \] 

where \( Q_m \) is blood flow to the tissue and \( Q_r \) is the withdrawal rate of the reference blood 
sample. Total blood flow (ml/min) was calculated by multiplication 
of blood flow per gram of tissue by organ weight. Average placental 
flow, total uterine flow, total utero-placental flow, and total renal flow 
were then calculated.

Statistical analysis. Data are expressed as means ± SE unless 
otherwise stated. Q-Q plot was used to determine whether the data 
were normally distributed. Relationships between MAP, PRA, and 
uteroplacental blood flow across gestation were assessed by Pearson 
bivariate correlation analyses. The effects of treatment across time on
maternal MAP and PRA were determined by 1-way repeated-measures ANOVA with Bonferroni post hoc corrections where appropriate. Maternal body weight, kidney weight, and uterine weights were assessed by 1-way ANOVA with Bonferroni post hoc corrections. Linear mixed-model repeated-measures ANOVA was employed to assess the effect of treatment group on fetal and placental weights and utero-placental blood flows, with litter size as a covariate where appropriate. This analysis uses the mother as the subject and the fetal and placental parameters as repeated measures of the mother to account for the similarity in factors within mothers and differences between mothers and groups. This analysis also generates estimated marginal means, which are used when representing these data. Sidak post hoc corrections were used for pairwise multiple comparisons between treatment groups. Data were analyzed using SPSS version 17 (SPSS, Chicago, IL). P < 0.05 was considered statistically significant.

RESULTS

Maternal measurements. Maternal MAP and PRA were not significantly different between the sham, 2K-1W, and 2K-2W groups prior to surgery (control; Fig. 1). Across gestation, maternal MAP was significantly increased in the 2K-1W group (~15 mmHg at GA0 and ~7 mmHg at GA28; both P < 0.05) compared with the sham group. In the 2K-2W group, MAP was also increased across gestation (~25 mmHg at GA0 and 20 mmHg at GA28, both P < 0.05) compared with the sham group. MAP was greater in the 2K-2W group than in the 2K-1W group (Fig. 1). Maternal PRA was significantly different between the sham, 2K-1W, and 2K-2W groups prior to surgery (control; Fig. 1). Across gestation, maternal body weight was ~23% less in the 2K-1W group compared with the sham group (~268% at GA0 compared with the sham group). In the 2K-2W group, MAP was increased in all groups at GA28 compared with their respective control values (all P < 0.05); however, PRA was not different between any of the groups at GA28.

Maternal body weight increased across gestation and was similar between the sham, 2-kidney-1-wrapped (2K-1W), and 2-kidney-2-wrapped (2K-2W) groups. On GA28, maternal body weight was 3.3 ± 0.2 kg in the sham group, 3.5 ± 0.1 kg in the 2K-1W group, and 3.7 ± 0.7 kg in the 2K-2W group. Total maternal kidney weight was 18.6 ± 1.0 g in the sham group, 20.9 ± 0.9 g in the 2K-1W group and 22.9 ± 1.2 g in the 2K-2W group. In the 2K-1W group, there was no difference in total kidney weight or total kidney weight per gram of body weight (7.9 ± 0.6 g) compared with the sham group (5.7 ± 0.2 g). However, right kidney weight per gram of body weight was increased in the 2K-1W group (3.3 ± 0.1 g) compared with the right kidney per gram of body weight in the sham group (2.9 ± 0.1 g), reflecting the compensatory increase in nonwrapped kidney size in the 2K-1W group. In the 2K-2W group, total kidney weight was significantly increased compared with the sham (P < 0.05) but not when kidney weight was corrected for maternal body weight (6.1 ± 0.3 g).

Fetal and placental measurements. Litter size was similar between the sham (4 ± 1 pups/litter), 2K-1W (4 ± 1 pups/litter), and 2K-2W (4 ± 1 pups/litter) groups. There were no significant differences in fetal body weight or placental weight between the sham, 2K-1W, and 2K-2W groups (Fig. 2). However, fetal-to-placental weight ratio was increased by ~12% (P < 0.01) in the 2K-1W group compared with the sham group (Fig. 2), but it was similar between the sham and 2K-2W groups (Fig. 2). Total uterine weight and total uterine weight per gram of body weight were similar between groups (data not shown).

Placental and renal blood flows. Placental blood flow per gram of tissue (ml·min⁻¹·g⁻¹) was ~11% less (P = 0.09, unpaired t-test with Bonferroni correction), and total placental blood flow (ml/min) was ~12% less (P = 0.08) in the 2K-1W group compared with the sham group (Fig. 3). Placental blood flow per gram of tissue (ml·min⁻¹·g⁻¹) was ~42% less (P < 0.05) and total placental blood flow (ml/min) was ~51% (P < 0.05) less in the 2K-2W group compared with the sham group (Fig. 3). Uterine blood flow (flow to the uterine muscle wall) comprised ~40% of the total utero-placental blood flow and was not different between the groups (data not shown).

There were no differences in total renal blood flow between the sham (151 ± 13 ml/min), 2K-1W (100 ± 14 ml/min), and 2K-2W (91 ± 22 ml/min) groups. In the sham group, renal blood flow per gram of tissue was similar between the left (4.1 ± 0.4 ml·min⁻¹·g⁻¹) and right kidney (4.2 ± 0.6 ml·min⁻¹·g⁻¹) (Fig. 4). In the 2K-1W group, renal blood flow per gram of tissue in the left kidney was lower compared with the right kidney (1.8 ± 0.3 ml·min⁻¹·g⁻¹ and 3.6 ± 0.6 ml·min⁻¹·g⁻¹, respectively; P < 0.05); this resulted in a ~35% (P < 0.05) reduction in total renal flow per gram of tissue in the 2K-1W group compared with the sham group. In the 2K-2W group, left renal blood flow (2.1 ± 0.5 ml/min/g) was similar to the right renal blood flow (1.8 ± 0.6 ml·min⁻¹·g⁻¹); however, total renal blood flow per gram of tissue was ~53% (P < 0.05) less in the 2K-2W group compared with the sham group.

Fig. 1. Maternal mean arterial pressure (MAP; mmHg; top), and plasma renin activity (PRA; ng ANG 1·ml⁻¹·h⁻¹; bottom) for sham (black), 2-kidney-1-wrapped (2K-1W; light gray) and 2-kidney-2-wrapped (2K-2W; dark gray) groups on the control day (presurgery), gestational day 0 (GA0), and gestational day 28 (GA28) (of a 32-day gestation). Values are expressed as means ± SE. The letters refer to a repeated-measures ANOVA with Bonferroni post hoc comparisons; P < 0.05 for all dissimilar letters.
Relationships between utero-placental blood flow and maternal characteristics. No significant correlations between fetal weight, placental weight, and utero-placental blood flow and MAP (GA0 or GA28) and PRA (GA0 or GA28) were observed in the sham group. In the 2K-1W group, MAP at GA0 (r = 0.71, P < 0.01), PRA at GA0 (r = 0.52, P < 0.01) and PRA at GA28 (r = 0.58, P < 0.01) were positively correlated with utero-placental blood flow. In the 2K-2W group, MAP at GA28 was negatively correlated with utero-placental flow (r = −0.69, P < 0.01), whilst PRA at GA28 (r = 0.63, P < 0.01) was positively correlated with utero-placental flow in the 2K-2W group.

DISCUSSION

This study has shown that moderate maternal hypertension was associated with decreased placental blood flow in rabbits. However, mild hypertension was not associated with a significant decrease in placental blood flow, though placental efficiency as measured by fetal-to-placental weight ratio in this group increased. Neither moderate nor mild maternal hypertension, were associated with changes in fetal body weight. These findings are similar to the changes observed in human hypertensive pregnancies, showing that some, but not all, pregnancies complicated by hypertension and/or intrauterine growth restriction (IUGR) are associated with reduced utero-placental blood flow (52).

In these studies, we utilize two models to examine hypertension in pregnancy. In the current study, in agreement with our previous reports, these models were characterized by increased arterial pressure, ~15 mmHg in the 2K-1W and ~25 mmHg in the 2K-2W group prior to pregnancy, with all groups demonstrating a modest reduction in arterial pressure across...
gestation (32, 34). Maternal PRA was increased at GA0 in the mild hypertensive group in agreement with our previous studies (16, 32). PRA increased throughout gestation in all groups, as previously observed in both rabbit (32) and human pregnancies (4, 6); thus by late gestation, there was no difference in maternal PRA between the groups. In the current study, for the first time, we report that renal blood flow is reduced by ~35% in the 2K-1W model and ~53% in the 2K-2W model, confirming that these rabbit models of maternal hypertension are associated with renal dysfunction. We also report that in late gestation, renal blood flow in the pregnant normotensive rabbit was 8.3 ml-min\(^{-1}\cdot g\)\(^{-1}\), a level that is double that of RBF (~4 ml-min\(^{-1}\cdot g\)\(^{-1}\)) in nonpregnant female rabbits (17). This greater renal blood flow in the pregnant rabbit is consistent with human studies that have shown a doubling in renal plasma flow throughout pregnancy (46). However, while the hypertensive animals had reduced renal function in late gestation compared with the sham group, based on the understanding that renal wrapping reduces renal blood flow from ~4 ml-min\(^{-1}\cdot g\)\(^{-1}\) to ~2 ml-min\(^{-1}\cdot g\)\(^{-1}\) in male rabbits (14, 15), we concluded that some degree of pregnancy-induced increase in renal function had also occurred in the hypertensive animals, given that RBF was 5.4 ml-min\(^{-1}\cdot g\)\(^{-1}\) and 3.9 ml-min\(^{-1}\cdot g\)\(^{-1}\) in the 2K-1W and 2K-2W pregnant rabbits, respectively. This is supported by studies in humans, showing that in pregnant women, mild renal disease is associated with similar changes in renal hemodynamics to those seen in healthy women, but these changes do not occur to the same extent (27). Renal disease, both with and without accompanying hypertension, is considered an important risk factor for adverse maternal and fetal outcomes, including IUGR and the development of pre-eclampsia (10, 19, 43).

We have previously shown that these models of mild and moderate hypertension differentially alter placental structure and placental gene expression of the renin-angiotensin system without affecting fetal growth (34) and altered renal development in young offspring (32). We have also demonstrated that programming of hypertension in adult offspring in the 2K-1W (13, 16), although it should be noted that MAP was increased ~30 mmHg in the 2K-1W mothers in those studies, a level greater than that achieved in the current study. The arterial pressure of offspring of 2K-2W mothers has yet to be followed into adulthood. In the current study, the microsphere method was used to measure blood flows. Total placental flow in the normotensive animals was ~3.5 ml/min, which is consistent with previous studies showing that the average rabbit placental blood flow on GA24 was ~2.5 ml/min and on GA30 was ~4.5 ml/min (23); total placental blood flow at GA29 was ~25 ml/min (5), suggesting that our microsphere technique was accurately measuring utero-placental blood flows. These measures of utero-placental flow in the hypertensive rabbit mothers allow the connection of studies performed in the offspring of these models to predict that babies of human hypertensive pregnancies may also be at risk of future adult disease, despite normal birth weight.

In the mild hypertensive group, placental blood flow was not significantly different than that in the normotensive animals (~12%, \(P = 0.08\)), but fetal-to-placental weight ratio (a surrogate for placental efficiency) was increased. We have recently reported significant differences in placental structural differentiation and in placental gene expression in this model that may increase the placenta’s ability to deliver adequate nutrients and oxygen to the fetus that may compensate, at least to some degree, for the hemodynamic changes seen in the mild hypertensive group and thereby maintain fetal growth (34). Increased placental efficiency in other animal models, including sheep, rat, and mice, is thought to be caused by increased maternal nutrient availability, increased transplacental concentration gradients, and/or direct increases in the placental nutrient transfer capacity per gram of placenta, all resulting from placental metabolic modifications in response to the altered maternal environment (8, 21, 31, 36). However, we are yet to measure metabolic parameters and nutrient transport in hypertensive pregnant rabbits. Thus while placental blood flow was not decreased in the mild hypertensive group, placental efficiency may be modified due to changes in these factors, which, in turn, may alter nutrient and oxygen delivery to the fetus.

In the moderate hypertension group, placental blood flow was decreased by ~51%. This was not associated with changes in placental weight, fetal body weight, or placental efficiency. These findings are consistent with a previous study (26) conducted in renal clip hypertensive rats with severe hypertension (+60 mmHg), which showed a ~68% decrease in placental blood flow, without changes in fetal or placental weights. The decrease in placental blood flow was accompanied by an increase in resistance to flow in the placenta, suggesting regional vasoconstriction (26). This is in contrast to a study in normotensive sheep that showed that placental blood flow progressively increased across gestation and was associated with a progressive decrease in vascular resistance, due to the progressive increase in cross-sectional area of the uterine vascular bed across gestation (7). Our data (34) and that of Karlsson et al. (26) suggest that alterations to placental morphology earlier in gestation may be implicated in the late-gestation reduction in placental blood flow seen in the hypertensive animals by affecting placental vascular resistance. Again, this is in contrast to the normal correlation between growth of the placental blood vessels and placental blood flow, such that alterations in placental flow are likely to affect placental structural development, and vice versa (21).

In addition to the maternal renal dysfunction and increased MAP, maternal PRA was altered in the mild and moderate forms of maternal hypertension. Maternal PRA prior to pregnancy (GA0) was associated with utero-placental blood flow in the mild hypertensive group, but not the 2K-2W group. We have previously shown that both mild and moderate hypertensive groups had a significant reduction in placental renin mRNA expression during late gestation and that placental renin mRNA across gestation was negatively correlated with fetal and placental weight (34). While the role of the RAS during pregnancy is not well understood, several studies have suggested the utero-placental renin may be involved in the regulation of utero-placental flow (1, 2, 50), the mechanisms involved in the regulation of utero-placental flow by renin, the interaction between maternal renin and other utero-placental blood flow regulators such as kinins (2, 18, 47), and the interaction between placental renin and maternal renin still remain to be determined. It is also a possibility that agonistic auto-antibodies against the angiotensin type 1 receptor may be involved in the reduction of placental blood flow (11).

These studies suggest that mild-to-moderate maternal hypertension associated with maternal renal dysfunction can alter...
late-gestation placental function, which, in turn, may alter/ reduce the placenta’s nutrient and oxygen transfer capacity, independent of changes to fetal body weight. Placental insufficiency and nutrient restriction have been implicated as mechanisms in the intrauterine programming of adult disease (39, 40). This highlights the importance of further understanding the mechanisms associated between mild-to-moderate maternal chronic hypertension, placental development, and the long-term outcomes of the offspring (48).

Perspectives and Significance

Human pregnancies associated with hypertension and renal diseases have been shown to be associated with alterations in utero-placental perfusion and fetal growth. However, the long-term outcome of human pregnancies complicated by mild-to-moderate maternal hypertension remain unknown. Our studies suggest that children from pregnancies complicated by even mild to moderate maternal hypertension, with obstetric outcomes at birth not outwardly different to normotensive pregnancies, may have an increased risk of cardiovascular disease in adult life.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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