# Reduced Uterine Perfusion Pressure (RUPP) Increases Mean Arterial Pressure in Pregnant Dams, But Has No Effect On Brain Weight In Dams Or Their Offspring

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**ABSTRACT**

*Preeclampsia is a disorder that occurs during a woman's pregnancy. Its main symptom is hypertension. Previous studies have used a reduced uterine perfusion pressure (RUPP) model to mimic hypertensive conditions. A RUPP model was achieved by inducing hypertension through the insertion of a clip around the abdominal aorta in dams (pregnant rats). Arterial pressure was measured and recorded in the control (NP) and RUPP dams. The results showed that the RUPP dams experienced a decrease in body weight from the time of surgery to the time of death. In addition, the mean arterial pressure increased in RUPP dams compared to that of the NP dams.*

## Introduction

Preeclampsia (PE), also known as toxemia, occurs during a woman's pregnancy and postpartum period, and affects approximately 5-7% of pregnancies (Srinivas *et al*., 2009). It is often characterized by an increase in blood pressure (hypertension), as well as excessive amounts of protein in the urine (proteinuria). Other symptoms of PE include a rapid increase in weight gain, abdominal pain, decrease in urine output, and excessive vomiting and/or nausea (Wang *et al*., 2009)). In general, slight variations in blood pressure are normal; in the absence of preeclampsia a number of mechanisms work to counteract these variations to keep blood pressure within a healthy range (Marieb & Hoen, 2010). In women with preeclampsia, significant hypertension is observed, specifically during the second and third trimesters (Wang *et al*., 2009). Some women may be at higher risk for PE than others. Risk factors for developing preeclampsia include obesity (Mbah *et al*., 2010), a history of chronic hypertension and/or PE in past pregnancies (Canti *et al*., 2010), a history of various diseases or disorders such as diabetes or rheumatoid arthritis, or a pregnancy over the age of 35 years (Wang *et al*., 2009). Unfortunately, there are no predetermined warnings or patterns as to whether or not the symptoms of PE will remain steady, digress, or progress into eclampsia. The effects of preeclampsia typically cease after giving birth, but there may be some effects that continue into the postpartum period, such as continued hypertension (Canti *et al*., 2010), a decrease in brain size (Oatridge *et al*., 2002), kidney disease, and insulin resistance combined with reduced vascular elasticity (Suzuki *et al*., 2008). Other long-term effects may include focal segmental glomerulosclerosis, nephropathy and nephrosclerosis, though these may also be found in women who have not experienced PE during pregnancy (Suzuki *et al*., 2008). Causes and potential preventative measures have yet to be determined.

Although there are no cures for preeclampsia, aside from delivery of the baby, there are some preventative measures that can be used, such as medications for hypertension (Costantine *et al*., 2010), and exercise (Yeo & Davidge, 2004). Medications used to reduce the risk of PE include magnesium sulfate, methyldopa, hydralazine, and labetalol (McCoy and Baldwin, 2009). Magnesium sulfate is typically favored because it increases arterial compliance, leading to a decrease in pressure within the vessels (Rogers *et al*., 2010), as well as aiding in the prevention of hypertensive encephalopathy (Belfort *et al*., 2008). Statins (i.e. pravastatin) may also be considered for the prevention of the vascular abnormalities of PE (Constantine *et al*., 2010). Regular exercise before pregnancy may help, as the heart and blood vessels are conditioned and stronger (Yeo & Davidge, 2004). Exercise also produces and enhances natural antioxidants within the body, reducing oxidative stress and potential chances of developing preeclampsia (Yeo & Davidge, 2004). In general, physical activity increases cardiovascular

health, causes a decrease in hypertension, and alters neuronal activity in the caudal hypothalamus (Kramer *et al*., 2000).

High blood pressure during pregnancy should not be the only concerning aspect of PE. While most symptoms of preeclampsia cease after giving birth, there can be some long-term effects. Women who have suffered from preeclampsia seem to be at higher risk for hypertension and cardiovascular disease later in life (Gilbert *et al*., 2008i). Other studies suggest that patients who had suffered ten or more years earlier had higher blood pressure, body mass and weight accumulation around the mid-section (Canti *et al*, 2010). Preeclamptic mothers have also been shown to have a significantly smaller brain size during pregnancy and after giving birth (Oatridge *et al*, 2002), as well as having a higher risk for stroke later in life (Brown *et al*., 2006). Babies born under preeclamptic conditions have been known to have a smaller head circumference and tend to be at higher risk for stroke (Kajantie *et al*., 2009). In addition, PE has been associated with neonatal encephalopathy, a disease that alters brain function or structure (Impey *et al*., 2001); neonatal encephalopathy may be caused by cerebral vasoconstriction (Impey *et al*., 2001).

High blood pressure is one characteristic of preeclampsia. Blood pressure refers to the force per unit area exerted on a vessel wall by the blood within it, and usually implies systemic arterial blood pressure. Pressure gradients within the vascular system keep blood moving; high pressure results when there is a form of resistance present. Resistance may be attributed to various factors, such as a narrowing of the arteriole walls, an increase in blood volume or viscosity, or shorter blood vessel length (Marieb & Hoehn, 2010). Maintaining a homeostatic balance of many variables is essential to life; blood pressure is one such variable. Hypertension is observed in about one-third of adults in the United States (Centers for Disease Control and Prevention, 2008); contributing factors may include, but are not limited to, a high intake of salt or saturated fats, diabetes, stress, and smoking (Marieb & Hoehn, 2010).

An intricate system of feedback loops regulates blood pressure within the body every day (Figure 1, Appendix A). The medulla oblongata is the control center for homeostatic reflexes including blood pressure. A region within the medulla oblongata, the nucleus tractus solitarious (NTS), is the primary site of cardiorespiratory reflex integration (Colombari *et al*., 2001). Disturbances or damage within the NTS can result in an increase of arterial pressure or sustained hypertension (Colombari *et al*., 2001). Increases in blood pressure initiate a feedback loop that begins within the blood vessels. Baroreceptors within the carotid arteries and aortic arch detect changes in blood pressure (Marieb & Hoehn, 2010). When blood pressure increases, baroreceptors are activated and impulses are sent to the vasomotor center of the brain, a cluster of neurons within the medulla oblongata that tonicly constrict blood vessel diameter. Activation of baroreceptors inhibits the vasomotor center, causing dilation of blood vessels and a corresponding reduction in blood pressure (Marieb & Hoehn, 2010). Within the vasomotor center are the rostral ventrolateral medulla (RVLM) and caudal ventrolateral medulla (CVLM). The RVLM contains neurons that work to generate and maintain resting levels of blood pressure (Cravo *et al*., 2003). Inputs may be received by the RVLM neurons from neurons located within the CVLM and NTS (Dampney *et al*., 2003). The CVLM contains neurons that receive inputs from baroreceptors and control the RVLM; a lack of inhibitory action results in hypertension (Colombari *et al*., 2001). However, some studies suggest that the CVLM also inhibits RVLM sypmathoexcitatory neurons even if not triggered by baroreceptors (Sved *et al*., 2000). In addition, the CVLM may be inhibited regardless of baroreceptor reflexes, causing an increase in blood pressure, suggesting that the CVLM may function independently of baroreceptor input (Sved *et al*., 2000).

In addition to the baroreceptor reflex, hormones play a role in controlling blood pressure. The effects of norepinephrine (NE), angiotensin II, and antidiuretic hormone (ADH) increase blood pressure, whereas the effect of atrial natriuretic peptide (ANP) reduces blood pressure (Marieb & Hoehn, 2010). Norepinephrine is released when the sympathetic nervous system is activated, increasing the heart rate, cardiac output and vasoconstriction, resulting in an increase in blood pressure. Angiotensin II is generated from renin, a hormone released by the kidneys when blood volume decreases (Marieb & Hoehn, 2010). Like NE, angiotensin II causes an increase in blood pressure through vasoconstriction. It also aids in increasing blood volume by stimulating the release of aldosterone and ADH (Marieb & Hoehn, 2010). Atrial natriuretic peptide is produced within the heart's atria when there is an increase in blood pressure.

It inhibits secretions from renin and aldosterone, and promotes the secretion of salt and water from the kidneys, decreasing blood pressure. Unlike the previous two hormones, ANP is a vasodilator. ADH (or vasopressin) is produced by the hypothalamus and, as opposed to ANP, it causes the kidneys to reabsorb water. If solute concentrations are high within the blood, osmoreceptors send impulses to neurons within the hypothalamus and ADH is released, inhibiting the formation of urine. If concentrations are low, ADH is not released and water loss is permitted (Marieb & Hoehn, 2010). As one can conclude, the regulation of blood pressure is complex, involving many factors.

Previous studies have used the reduced uterine perfusion pressure (RUPP) model to study hypertension. A RUPP model is achieved by inducing uteroplacental ischemia, as it reduces blood flow, thus leading to hypertension that most resembles preeclamptic conditions (Granger *et al*., 2006). Studies use this model to observe changes in vascular reactivity (Walsh *et al*., 2009), as the model is associated with an increase in mean arterial pressure (MAP) and a reduction in kidney function (Alexander *et al*., 2001); increasing arterial pressure increases vascular resistance, thus leading to an increase in hypertension (Crews *et al*., 2000). Some studies suggest that RUPP inhibits vascular relaxation, which is endothelium-dependent and requires the release of nitrous oxide and cGMP production within systemic vessels, which could potentially explain vascular resistance (Crews *et al*., 2000). In addition, RUPP fetuses tend to be lighter in weight and fewer in number when compared to non-RUPP pregnancies (Gilbert *et al*., 2007).

Human data suggests preeclamptic mothers have a reduced body and brain weight (Oatridge *et al*., 2002), as well as their offspring's body weight (Wust *et al*., 2005). The present study was designed to investigate these variables using the RUPP model. Furthermore, because renal and adrenal hormones are so tightly linked to blood pressure regulation, we measured kidney and adrenal gland weight. We hypothesized that mean arterial pressure would be increased in RUPP dams, body and brain weight would be reduced, and kidney and adrenal weight would increase. Additionally, we hypothesized that RUPP fetuses would have reduced body and brain weight.

## Methods

Two groups of rats were obtained for this experiment from the University of Minnesota-Duluth, a normal pregnant group, which served as the control, and a RUPP group. On day 14 of gestation, after being anesthetized both groups underwent surgery, as to ensure the surgical procedure would not be cause for error in one model or the other. An incision was made down the midline of the body in both groups, and a clip was inserted around the abdominal aorta above the iliac bifurcation in the RUPP model, as well as on the branches of the right and left ovarian arteries (Gilbert *et al*., 2007; Figure 2). The incisions were closed and the rats were allowed to recover for five days. Following recovery, both the control and RUPP groups were anesthetized and instrumented with carotid catheters (Gilbert *et al*., 2007). The catheters were drawn around the back of the neck and exteriorized after implantation. After recovery, the insertion of a catheter allowed for the measurement of arterial pressure once connected to a pressure transducer (Gilbert *et al*., 2007); arterial pressure was measured and recorded. The rats were humanely euthanized, and the pups were removed, blotted dry, and weighed (Gilbert *et al*., 2007). The brains from both groups of mothers and pups were removed, blotted dry, and weighed, as well as the adrenal glands from the mothers.

## Results

Studies have shown that RUPP dams are lighter in body weight than NP dams (see Joyner *et al*., 2007). Results from the present experiment supported our hypothesis; compared to the NP dams, the RUPP dams experienced a decrease in body weight from the time of surgery to the time of death (NP 307.00 ± 11g vs. RUPP 320.25 ± 7.2g $p < 0.05$; Figure 3).

We hypothesized that mean arterial pressure (MAP) would increase in RUPP dams when compared to NP dams. Our data support the hypothesis (NP 88.67 ± 1.50mmHg vs. RUPP 106.25 ± 2.80mmHg, $p<0.05$; Figure 4).

We hypothesized that RUPP dams would have smaller and fewer pups than NP dams; however, the data does not support the hypothesis. There was no difference observed in body weight between offspring of NP dams or RUPP dams (NP offspring 2.34 ± 0.08g vs. RUPP offspring 2.266 ± 0.058g, $p>0.05$; Figure 5). Additionally, there was no difference in the number of fetal absorptions between the NP dams and RUPP dams (NP 0.75 ± 0.25 vs. RUPP 5 ± 2.2, $p>0.05$; Figure 6).

We hypothesized that brain weight would decrease in both RUPP dams and pups compared to NP dams and pups. We observed no difference in brain weight in either dams (NP 2.0151 ± 0.037g vs. RUPP 1.890 ± 0.055g, $p>0.05$; Figure 7) or pups (NP 0.1215 ± 0.005g vs. RUPP 0.1187 ± 0.0058g, $p>0.05$); Figure 8).

There was no change in kidney weight between NP and RUPP dams as was hypothesized (*Left*: NP 0.87 ± 0.044g vs. RUPP 0.86 ± 0.019g, $p>0.05$; Figure 9. *Right*: NP 0.892 ± 0.053g vs. RUPP 0.8975 ± 0.018g, $p>0.05$; Figure 10). In addition, neither the NP nor RUPP dams exhibited a change in adrenal weight (NP 0.05 ± 0.0091g vs. RUPP 0.0575 ± 0.0110g, $p>0.05$; Figure 11). We hypothesized an increase in kidney and adrenal weight.

Significant results were observed specifically in terms of MAP and body weight within the RUPP dams, thus supporting the hypothesis. The brain, kidney and adrenal weights within the RUPP dams, however, did not support the hypothesis. Furthermore, data from the fetal reabsorptions and fetal body and brain weights did not support our hypotheses.

## Discussion

The present experiment was designed to examine changes in physiological markers following reduced uterine perfusion pressure that mimics preeclampsia in humans. The primary findings of this study were a reduction in body weight and increase in MAP in pregnant dams that underwent RUPP. These results were expected, and in fact are characteristic of the RUPP model (for review, see Gilbert *et al*., 2008ii). Because of the complex regulation of blood pressure, we decided to grossly examine structures that may contribute to the disregulation of blood pressure in preeclampsia, namely the brain and kidneys. Furthermore, we examined reabsorption of the pups, as well as fetal body and brain weight.

The data presented supports the hypothesis that RUPP dams exhibit an increase in MAP and a decrease in body weight. Other studies have observed the same results and support the hypothesis (see Joyner *et al*., 2007; Gilbert *et al*., 2007). We expected the RUPP model to have an increase in arterial pressure due to the surgical procedure that induced hypertension; the clip was inserted so as to reduce blood flow within the vessels, thus leading to hypertension that most resembles preeclamptic conditions (Granger *et al*., 2006).

The other factors within the study did not support the hypothesis as expected. The body weight of RUPP offspring, for example, has been shown to decrease considerably in previous studies (see Gilbert *et al*., 2007; LaMarca *et al*., 2008; Joyner *et al*., 2008), whereas our results showed no change when compared to the NP pups. This may have been due to the insufficient number of available dams, as most studies use seven to twenty subjects, whereas we had three or four. In addition, human error may have affected the weight in the duration of gestation; after the study, it was determined that one dam had been sacrificed on day 17 of gestation, while the other dams were sacrificed on day 19. This would reduce the RUPP pups' growth period by two days. An increase in reabsorption of RUPP pups was also hypothesized, but not supported in the results; RUPP dams typically give birth to fewer pups due to higher reabsorption rates than NP dams (Gilbert, unpublished date). A greater sample size may have demonstrated otherwise.

Preeclamptic human subjects have exhibited a decrease in brain size in previous studies (Oatridge *et al*., 2002). By using a RUPP model in rats, the same results were expected. However, no significant decrease was observed between the NP and RUPP dams. It is possible that neural regulation of blood pressure is altered in the RUPP model; however, our gross measurement of the brain weight may not have been sensitive enough to detect such changes. Had measurements been taken on a microscopic level, focusing on molecular and chemical changes, we may have been able to observe differences between the groups. Further investigations could use the immediate early gene cFos, a marker of neural activity, which

would show specific changes in brain activity involved in hypertension. Previous studies examining a genetically induced hypertension found that an increase in blood pressure that activates baroreceptors induces the expression of cFos within the NTS (Chan et al., 2003). In addition, nitric oxide synthase (NOS) decreases Fos within the NTS following baroreceptor activation, suggesting that NOS contributes to blood pressure regulation (Chan *et al*., 2003). In conscious rabbits, an increase in blood pressure increases cFos expression in neurons within the RVLM, CVLM and NTS (Dampney *et al*., 2003). These studies suggest that cFos would be a useful method to examine changes in brain activity that may regulate hypertension in the RUPP model. Furthermore, NOS may be an additional marker that could be involved in the neural regulation of hypertension in the RUPP model.

In addition to RUPP dams, we hypothesized a decrease in brain size in RUPP offspring. Although other studies have found lower body weights within RUPP pups when compared to NP pups (see Joyner *et al*., 2007; LaMarca *et al*., 2008), there have not been studies that suggest a smaller fetal brain size in RUPP models.

The kidney and adrenal gland are important in regulating blood pressure. The kidney secretes renin, which is the first step in the renin-angiotensin system (RAS). The adrenal gland is a modified sympathetic ganglion and secretes NE, a potent vasoconstrictor. Both systems rely on negative feedback to inhibit release of their products. It is possible that negative feedback in one or both of these systems is altered in the RUPP model. We hypothesized that a lack of negative feedback within the RAS of in RUPP dams leads to hypertrophy of kidney tissue, resulting in an increase of kidney weight. Additionally, we hypothesized that the a lack of negative feedback in the sympathetic nervous system led to hypertrophy of adrenal tissue, resulting in an increase in adrenal weight. Our data did not support these hypotheses. Further investigations could focus on measuring hormonal activity, such as NE and hormones in the RAS. Past studies have shown a decrease in angiotensin and angiotensin-converting enzyme (ACE), two components within the RAS, in RUPP dams versus NP dams (see Joyner *et al*., 2007). Furthermore, a decrease in kidney function has been observed in RUPP dams (see Gilbert *et al*., 2008ii). Hypertension induced by the hyperresponsiveness of the sympathetic nervous system has been observed in both rats and humans (Kontak *et al*., 2010; Samuelsson *et al*., 2010). Collectively, these studies suggest that both the kidney and adrenal gland are important components to examine when investigating hypertension; however, gross measurements of organ weight taken in the present study may not have been the optimal method.

In using a RUPP model to study the hypertensive effects resembling preeclamptic conditions, we found that MAP increases and body weight decreases in RUPP dams when compared to NP dams. The methods used to identify changes in RUPP fetuses did not reveal differences between groups in this study as hypothesized, nor were the changes identified in the kidneys and adrenal glands in the RUPP dams. Further investigation, accompanied with modifications in methods, may reveal a better understanding of the body (and brain's) blood pressure regulation under hypertensive conditions.

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## *Appendix A*

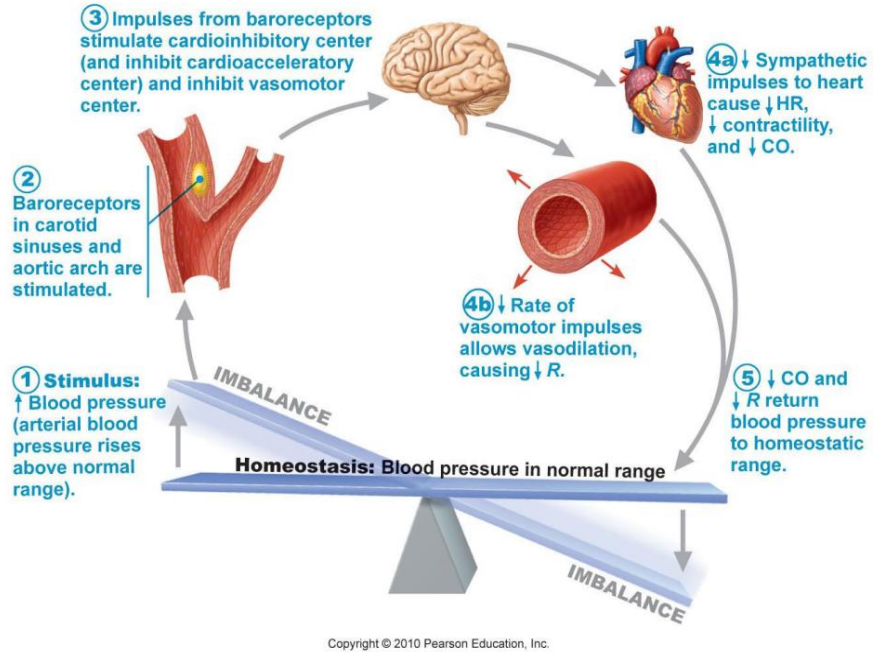


**Figure 1:** Blood pressure maintains a homeostatic balance through baroreceptor reflexes

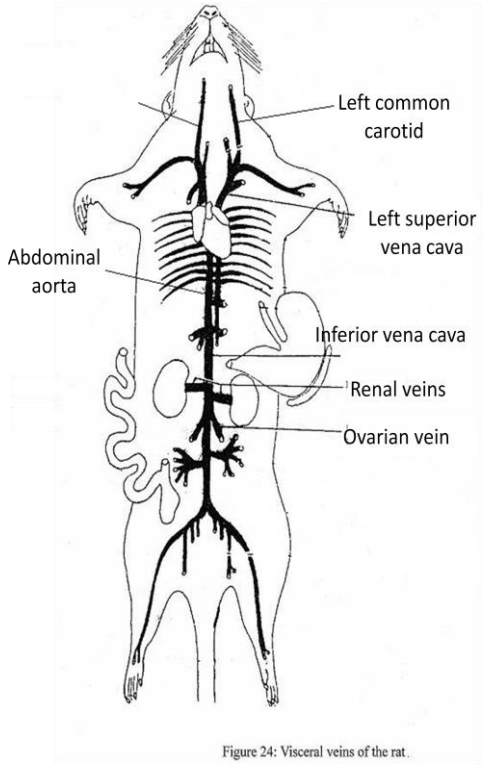


**Figure 2:** A schematic of vessels within a rat. Clips were inserted above the abdominal aorta and on the branches of the right and left ovarian arteries

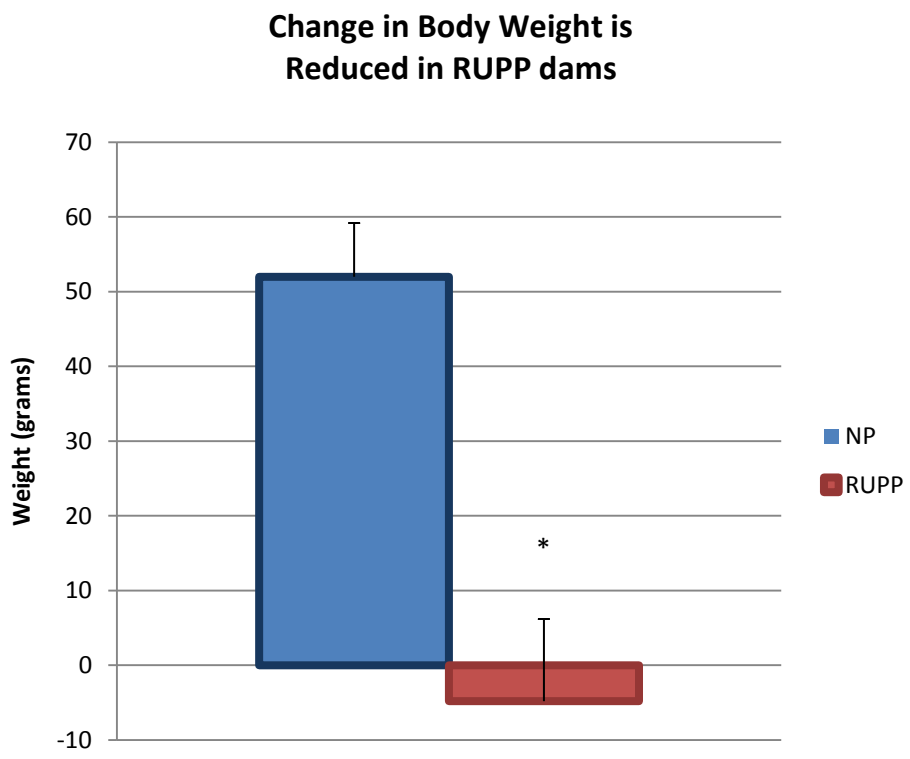


**Figure 3**: Change in body weight in dams from time of surgery to time of death (NP 52 ± 7.2g vs. RUPP -4.75 ± 11g; p<0.05)

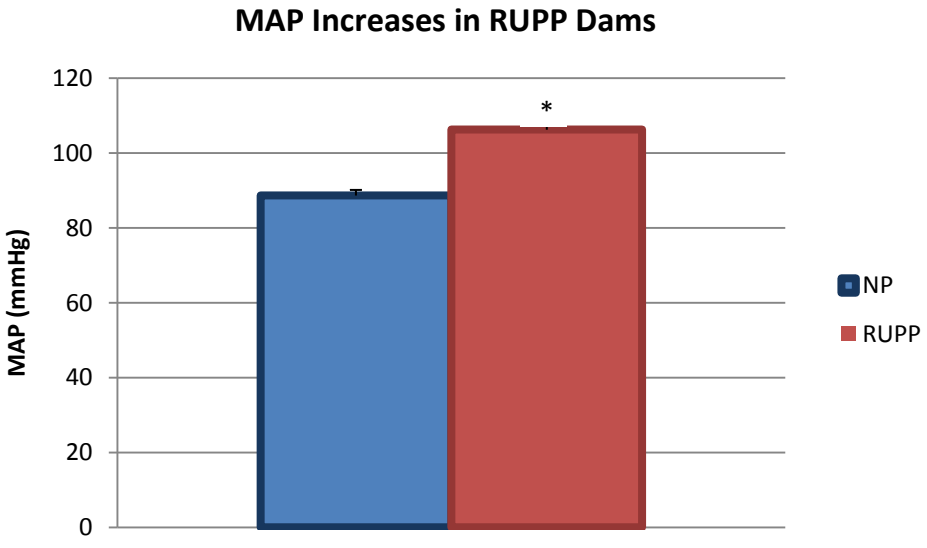


**Figure 4**: The mean arterial pressure (MAP) in dams (NP 88.97 ± 1.5mmHg vs. RUPP 106.25 ± 2.8mmHg; p<0.05)

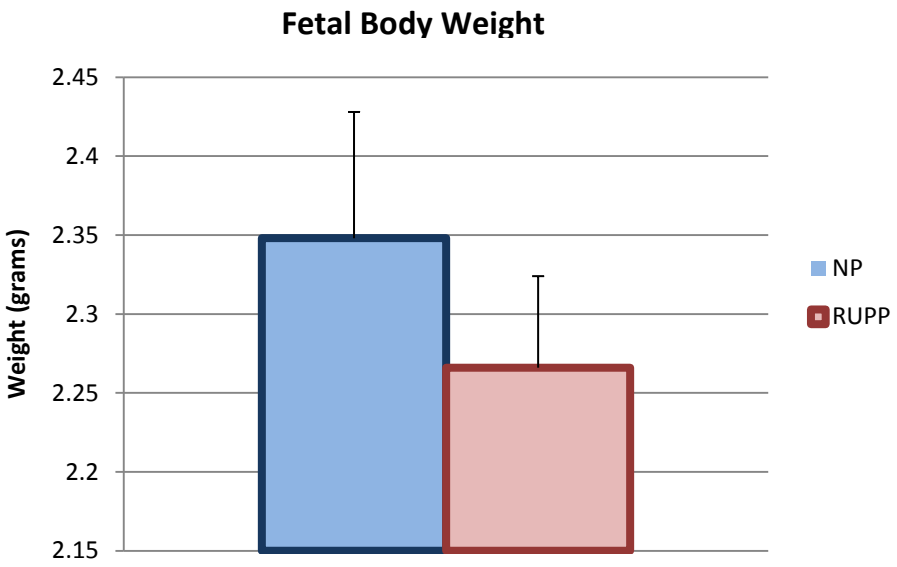


**Figure 5**: Fetal body weight at time of death (NP 2.348 ± 0.08g vs. RUPP 2.266 ± 0.058g, p>0.05

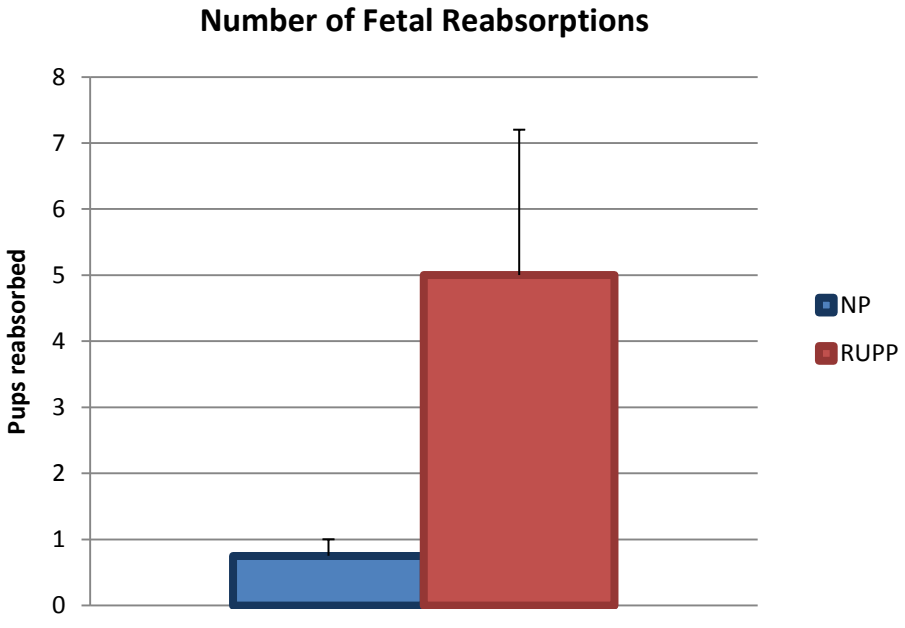


**Figure 6**: Average number of pups reabsorbed in dams (NP 0.75 ± 0.25 vs. RUPP 5 ± 2.2, p>0.05)

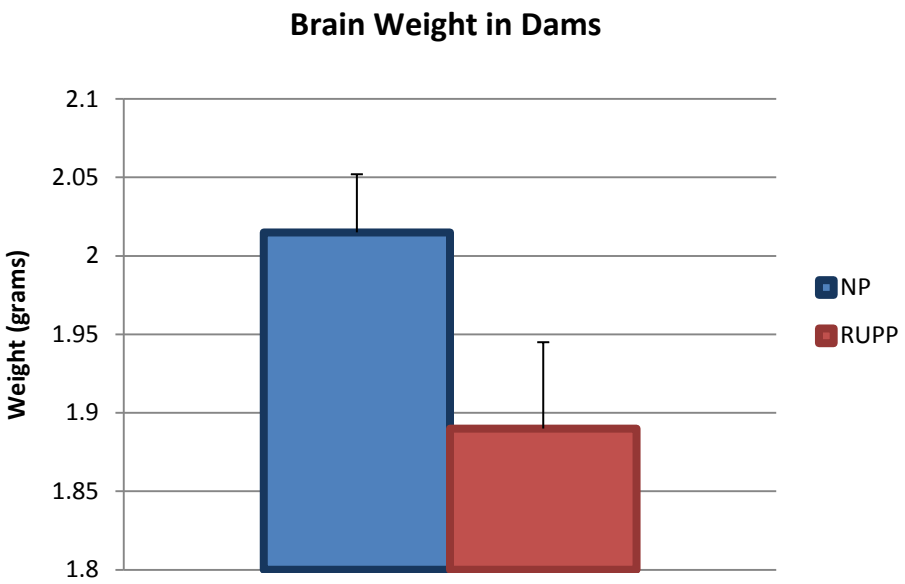


**Figure 7**: Brain weight of the dams at time of death (NP 2.0151 ± 0.037g vs. RUPP 1.890 ± 0.055g; p>0.05)

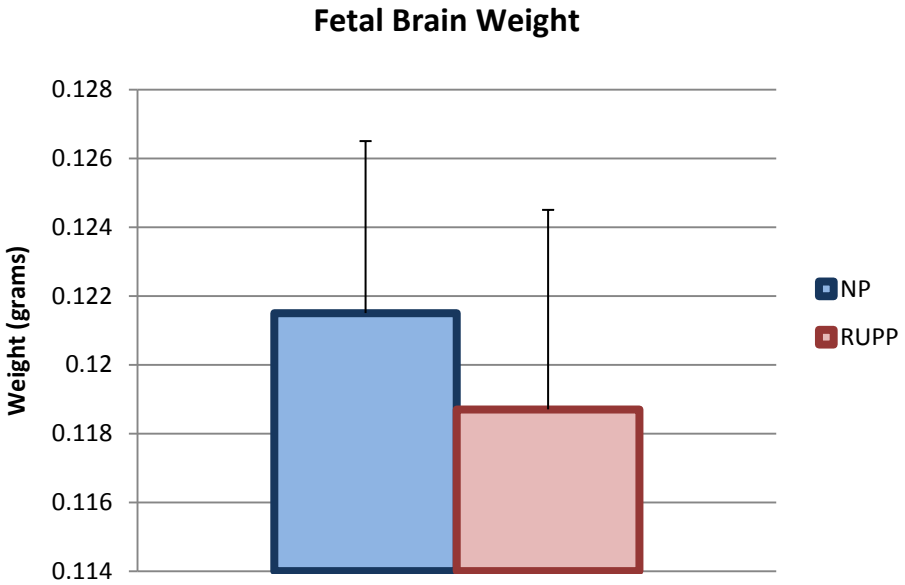


**Figure 8**: Fetal brain weight following death (NP 0.1215 ± 0.005g vs. RUPP 0.1187 ± 0.0058g; p>0.05)

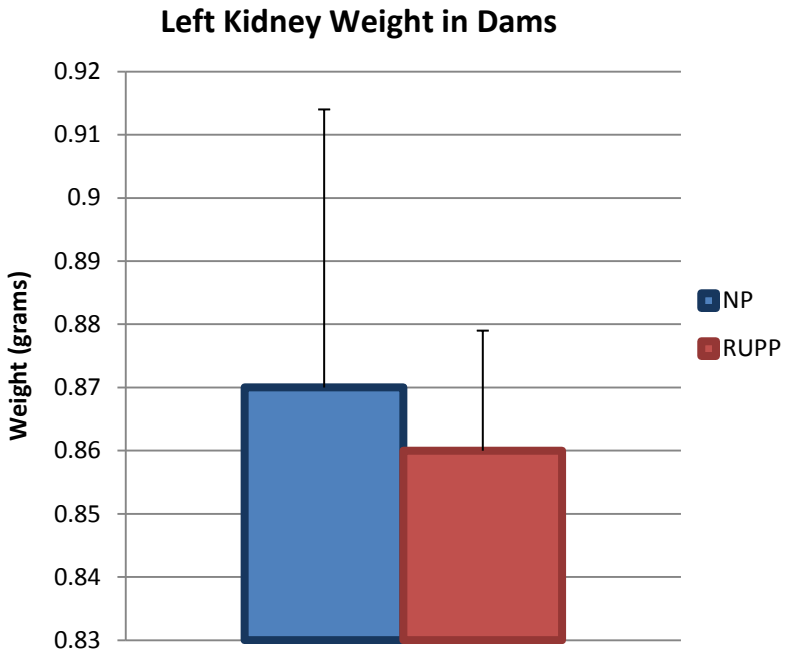


**Figure 9**: Average weight of the left kidney in dams (NP 0.87 ± 0.044g vs. RUPP 0.86 ± 0.019g, p>0.05)

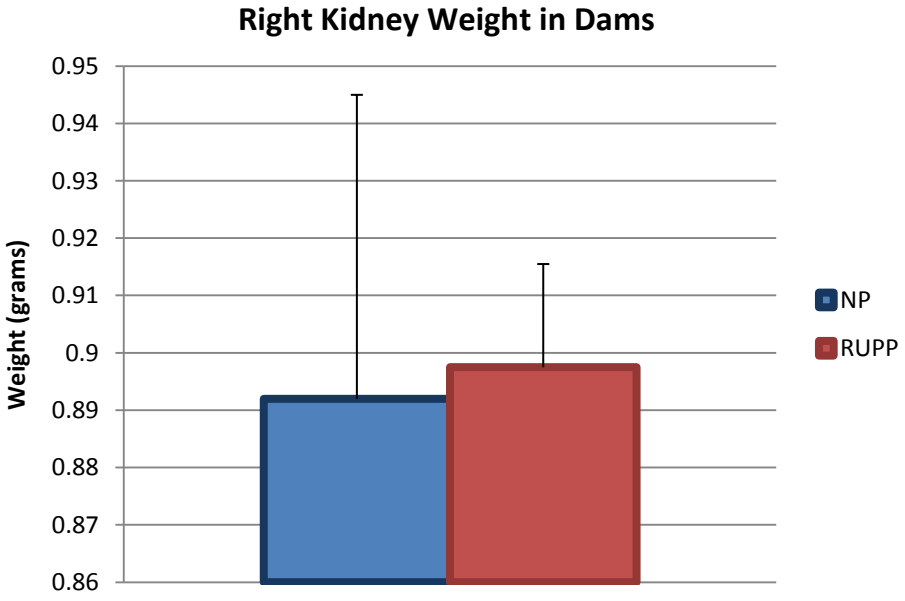


**Figure 10**: Average weight of the right kidney in dams (NP 0.892 ± 0.053g vs. RUPP 0.8975 ± 0.018g, p>0.05)

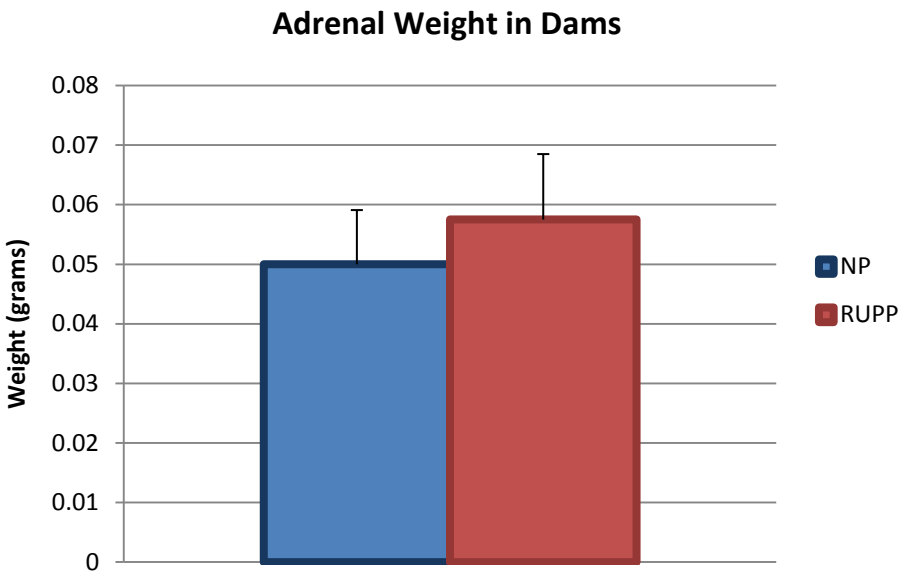


**Figure 11**: The average adrenal weight in dams at time of death (NP 0.05 ± 0.0091g vs. RUPP 0.0575 ± 0.011g, p>0.05)