Influence of intrauterine growth restriction on renal function in the adult rat

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Intrauterine growth restriction (IUGR) has been shown to influence renal development and lead to fewer nephrons. Data on long term renal function after IUGR are limited. We studied the effect on renal function of IUGR in aging rats. IUGR was induced using a model of bilateral uterine artery ligation in pregnant Wistar rats. Renal function was studied at the age of 18 months. In male IUGR rats, estimated glomerular filtration rate was significantly decreased compared to male control rats [1.1 (SD 0.3) 1.7 (SD 0.3) ml·min⁻¹, p<0.05]. Female IUGR rats showed an increased urinary protein excretion compared with female control rats [84 (SD 73) vs. 12 (SD 13) mg·24h⁻¹, p<0.01]. All male rats showed heavy proteinuria (p<0.01 vs. female rats from same experimental group), with no significant differences between the groups. Tubular reabsorption of phosphorus was lower in females, but showed no differences between the experimental groups. In conclusion, IUGR impairs renal function in the rat. It is suggested that a low nephron endowment leads to proteinuria as a sign of glomerular damage, and ends with a decrease in glomerular filtration rate as a sign of glomerular loss.

Key words: Renal function, Glomerular filtration rate, Proteinuria, Low birth weight, Intrauterine growth restriction.
In the last decade, evidence has mounted on the association between low birth weight (LBW) and an increased risk of chronic diseases such as hypertension, cardiovascular disease and diabetes mellitus in adulthood (1). According to the ‘fetal origin hypothesis’, intrauterine growth restriction (IUGR) not only results in LBW, but also reprograms the development of organs. This reprogramming is thought to be beneficial in the less favorable uterine environment, but may predispose to long-term problems later in life (1).

IUGR is associated with a low nephron endowment in humans (8, 9, 13), which has been confirmed in our animal model (16). The remaining nephrons compensate by hyperfiltration, which predisposes to develop glomerular and eventually systemic hypertension in later life according to the hyperfiltration theory (3, 4). The hyperfiltration and glomerular hypertension are a potential threat to the remaining nephrons, and may lead to proteinuria and glomerulosclerosis, with a further reduction in glomerular number. This starts a vicious cycle, which ends in renal failure.

However, data on renal function in late adulthood after IUGR are limited. Animal models are needed to study these long-term consequences of IUGR. Since the leading cause of IUGR in Western countries is uteroplacental insufficiency (7), an animal model using reduced uteroplacental blood flow will be the most appropriate model to study the effect of IUGR on renal function.

In order to study the long-term effect of IUGR on renal function, we investigated renal function in 18 months old rats with experimentally induced IUGR using a model of bilateral uterine artery ligation in the pregnant rat.

**Material and Methods**

Timed pregnant Wistar rats were obtained from Harlan CPB (Horst, The Netherlands) and housed in an animal room in the Clinical Animal Laboratory of the VU University Medical Center. A 12:12-h light-dark cycle was maintained in the room, at constant temperature and relative humidity. Rats had free access to tap water, and were fed a standard rodent chow *ad libitum*. All experiments were in accordance with the approval obtained from the Animal Welfare Committee (DEC) of the VU University Medical Center, Amsterdam.

IUGR was induced by bilateral ligation of the uterine arteries on day 17 of pregnancy as described previously (16, 17). Sham-operated dams underwent the same procedure except for the actual ligation. At day 21–22 of gestation pups were born. In order to improve survival of the small pups, litters were left undisturbed during the first 24 hours. Birth weight was defined as body weight measured 24-32 hours after birth. IUGR was defined as a birth weight under -2 SD of the mean of control pups (CTRL), born from sham-operated dams. All pups were cross-fostered and litters were reduced to 8-10 pups. At day 28 pups were weaned and housed 2 (males) or 3 (females) per cage. At regular intervals, body weight was measured.

To study renal function, blood and 24-hour urine samples were used. At the age of 18 months, rats were individually placed in a metabolic cage for collection of 24-hour urine. Afterwards, they were anesthetized with a mixture of ketamine HCl (75 mg/kg i.p.) and xylazine (5 mg/kg i.p.). Animals were weighed and length was measured from the nose to the tip of the tail. After taking a blood sample,