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Renal Regulation of Calcium-Phosphate Metabolism in Single- and Twin Pregnant Goats

Katarzyna MICHAŁEK, Małgorzata OŻGO and Wiesław Franciszek SKRZYPCZAK

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The aim of this study was the clearance assessment of renal function in single- and twin-pregnant goats and a comparison of selected parameters associated with calcium-phosphate management in terms of litter size. Clearance studies were carried out on 16 pregnant Polish White Improved goats (8 single pregnancies and 8 twin pregnancies). It was demonstrated that the kidneys of pregnant goats regulate the calcium-phosphate balance to a great extent. In spite of observed differences in parameters of renal functions, plasma calcium and inorganic phosphorus concentrations were comparable with normal reference values in further weeks of pregnancy. Significant differences in renal function between single and twin pregnancies were not observed. Gut absorption and/or bone tissue metabolism seem important for the maintenance of appropriate calcium-phosphate status.

Key words: Kidney, clearance, calcium, inorganic phosphorus.

Katarzyna MICHAŁEK, Małgorzata OŻGO, Wiesław Franciszek SKRZYPCZAK, Department of Animal Physiology and Cytobiology, West Pomeranian University of Technology, Dr Judyma 6, 71-466 Szczecin, Poland.
E-mail: katarzyna.michalek@zut.edu.pl
wieslaw.skrzypczak@zut.edu.pl
malgorzata.ozgo@zut.edu.pl

The maternal requirements for calcium and inorganic phosphorus increase along with the growth of the foetus(es) (SKRZYPCZAK *et al*. 1995; PRENTICE 2000). As a consequence, hormonal regulation undergoes adaptive changes. This particularly applies to parathormone, calcitriol, and calcitonin (GARNER *et al.* 1988; DE ROUFFIGNAC & QUAMME 1994; DAI *et al.* 2001; HUBERT *et al.* 2007; MUSCHER *et al.* 2008). In pregnant women, blood plasma concentrations of parathormone and calcitonin do not differ significantly from those observed in non-pregnant women (ARDAWI *et al.* 1997; MESTMAN 1998; PRENTICE 2000), whereas the level of calcitriol increases more than twofold. According to PRENTICE (2000), parathyroid hormone-related peptide, PTHrP, is the chief stimulating agent of 1á-hydroxylase activity in gestation. This peptide has only been detected in the blood plasma of pregnant and lactating females. It penetrates into the maternal circulation from the foetus, placenta, or mammary gland. In women, sheep, rabbits, and Guinea pigs, increased biosynthesis of active vitamin D_3 may also be a result of elevated concentrations of estradiol, prolactin, and placental lactogen (PRENTICE 2000). KOVACS and KRONENBERG (1997) have demonstrated that in pregnant rats, unlike the aforementioned species, parathormone is the main regulating agent of calcitriol biosynthesis. The concentration of these two calcitropic hormones increases simultaneously towards the end of gestation and the magnitude of this increase is dependent on the litter size (ARDAWI *et al.* 1997).

It has been observed in pregnant women, laboratory animals, sheep, and cows, that a decreased concentration of blood plasma calcium is closely related to the number of foetuses in the womb (MONIZ *et al.* 1985; ELIAS & SHAINKIN-KESTENBAUM 1990; ELZEN *et al.* 1995; CZAJKOWSKI 1996; JANKOWIAK *et al.* 1997; KOVACS & KRONENBERG 1997; SCHRŐDER *et al.* 1997; KALKKWARF *et al.* 1999). Plasma phosphorus concentration, on the other hand, does not change during pregnancy, neither in women nor in the females of other species, including goats (HUSAIN & MUGHAL 1992; PRENTICE 2000; SAREŁO *et al.* 2003). Concentrations of calcium and inorganic phosphorus in the blood plasma is a "resultant" of changes in the intestinal absorption, metabolism of osseous tissue, and renal excretion (DE ROUFFIGNAC & QUAMME 1994; ARDAWI *et al.* 1997). In women and laboratory animals, the enteric absorption of calcium and inorganic phosphorus during the early stages of gestation is twice as high as that of non-pregnant females (O'BRIEN *et al.* 2003). Also, reabsorption of the osseous tissue and renal excretion of these minerals increases (PRENTICE 2000). Urinal excretion of calcium in pregnant women increases from week 12, while in rats from the 2nd week of gestation, and results from, among other factors, increased glomerular filtration rate (GFR) and transient meal-induced hypercalcaemia. According to KOVACS and KRONENBERG (1997), a slight increase in calcium glomerular reabsorption during gestation does not fully compensate for the filtered load of Ca^{2+}. Thus, renal calcium management in pregnant women is not very economical, which also applies to inorganic phosphorus (PRENTICE 2000).

Renal regulation of excretion of calcium and inorganic phosphorus in small ruminants during pregnancy is not fully understood. There is a lack of information in the literature on this issue, especially in relation to litter size. Hence, this study is aimed at a clearance evaluation of the renal function in pregnant goats and at a comparison of changes in the parameters of calcium-phosphate metabolism regulation between single- and twin pregnancies.

Material and Methods

The experiment was carried out on 16 pregnant White Improved goats (8 single- and 8 twin pregnant does), aged 2-4 years. The animals did not exhibit any clinical symptoms of disease over the period of the studies. The goats were housed in individual pens, fed 3 times a day according to feeding standards (JARRIGE 1993), and had ad libitum hay, straw, and drinking water.

The does had been serviced naturally during their second heat (September/October), and births took place as expected (February/March). Samples of blood and urine were collected fortnightly from about one month before the planned service and over the first 3 months of gestation, and weekly during the remaining 2 months of gestation, always on the same day of the week.

The animals were weighed before feeding, and catheterized into the external jugular vein about 9.00 a.m., which allowed for quick and easy collection of 5 blood samples in short, 20-minute intervals; the catheter was also used for administration of a precise dose of inulin, the test substance (SKRZYPCZAK *et al.* 1995). In order to precisely measure the urinary flow rate (V), Foley catheters were placed inside the urinary bladders. After collecting the "zero" samples of blood and urine (B0 and U0, respectively), the animals were intravenously administered 20 ml of 10-% inulin solution (2 g inulin) at 10.00 a.m. Urine collection started after 10 minutes (U1, U2, U3, U4); the samples were taken in 20-minute intervals. We also drew a blood sample (B1, B2, B3, B4) in the middle of each interval. The blood was centrifuged immediately after collection, and the resulting plasma, as well as the urine samples, were frozen and stored at -20°C until analysis. The plasma and urine was used to measure the concentrations of calcium and inorganic phosphorus using the colorimetric method (Aqua-Medica laboratory biotests).

The following renal function parameters were calculated using the data: clearance (C), filtered load (F), tubular reabsorption (TR), and urinal excretion (UV) of calcium and inorganic phosphorus. Calcium F was calculated including its protein-bound fractions present in the blood plasma. We have assumed that 60% of calcium penetrates to the primary urine in the renal glomeruli (MANDON *et al.* 1993). The absolute values of the calculated renal function parameters were converted to 1 m^2 of the goat's body surface area according to Meeh (KETZ 1974):

$$BSA=0.106\cdot\sqrt{BW^2}$$

where: BSA – body surface area (m^2); BW – body weight (kg).

The results were grouped by the type and month of gestation. Means (m) and standard deviations (SD) were calculated. In order to test the significance of differences between renal function in each gestation period, as well as between the values of the same periods of single- and twin gestations, the data were subjected to a one-way ANOVA with the multiple-range test (Statistica 6.0 package).

Results

The resulting means, standard deviations, and significance of differences are presented in Tables 1 and 2. Total plasma calcium concentrations remained stable over gestation in both groups and ranged between 2.17 and 2.31 mmol/l (Table 1). Calcium clearance grew from 0.458 to 0.528 ml/min/m^2 over the first 4 weeks of gestation, followed by a decrease to 0.309 ml/min/m^2 in the 20th week of gestation, which was significantly ($P \leq 0.05$) lower compared to that observed in the first month (Table 1). In the goats with twin pregnancies, calcium clearance showed some variation, although without significance. In this group of goats, renal clearance of Ca^{2+} remained within the range 0.333-0.458 ml/min/m^2. The glomeruli-filtered load of calcium over gestation was rela-

Table 1

Calcium concentration in blood plasma (P) and clearance (C), glomerular filtration (F), tubular reabsorption (TR), and excretion with urine (UV) in single and twin pregnant goats

Week of pregnancy		P (mmol/l)		C (ml/min/m^2)		F (mmol/min/m^2)		TR (%)		UV (mmol/min/m^2)	
		single pregnant	twin pregnant	single pregnant	twin pregnant	single pregnant	twin pregnant	single pregnant	twin pregnant	single pregnant	twin pregnant
0	$\bar{x}$	2.31	2.31	0.458	0.458	0.078	0.078	98.02	98.02	0.0015^{c,d,E,F}	0.0015^{c,E}
(*A*)	SD	0.22	0.22	0.239	0.239	0.016	0.016	1.79	1.79	0.0014	0.0014
4	$\bar{x}$	2.23	2.21	0.528^{f}	0.376	0.082	0.085	97.79^{c,D,e,F}	98.56	0.0016^{c,d,E,F}	0.0009
(*B*)	SD	0.16	0.13	0.253	0.257	0.023	0.017	1.22	1.43	0.0009	0.0008
8	$\bar{x}$	2.26	2.24	0.339	0.346	0.075	0.075	98.98^{b}	98.94	0.0007^{a,b}	0.0007^{a}
(*C*)	SD	0.26	0.21	0.151	0.193	0.015	0.013	0.46	0.63	0.0003	0.0004
12	$\bar{x}$	2.27	2.25	0.347	0.418	0.078	0.083	99.05^{B}	98.83	0.0008^{a,b}	0.0010
(*D*)	SD	0.30	0.23	0.135	0.175	0.014	0.014	0.41	0.49	0.0003	0.0004
16	$\bar{x}$	2.30	2.20	0.318	0.333	0.091	0.080	98.90^{b}	99.23	0.0007^{A,B}	0.0007^{A}
(*E*)	SD	0.15	0.14	0.103	0.178	0.036	0.016	1.54	0.39	0.0003	0.0004
20	$\bar{x}$	2.26	2.19	0.309^{b}	0.368	0.075	0.085	98.99^{B}	99.11	0.0007^{A,B}	0.0010
(*F*)	SD	0.16	0.14	0.154	0.216	0.007	0.017	1.08	0.68	0.0003	0.0018
21	$\bar{x}$	2.22	2.17	0.343	0.442	0.074	0.086	98.73	98.83	0.0008	0.0010
(*G*)	SD	0.10	0.14	0.135	0.313	0.004	0.020	0.91	0.95	0.0003	0.0006

$\bar{x}$ – mean, SD – standard deviation;
a, b, c, d, e, f, – significance of differences ($P \leq 0.05$) of means in particular weeks of pregnancy;
A, B, D, E, F, – significance of differences ($P \leq 0.01$) of means in particular weeks of pregnancy;

tively stable in both groups and ranged within 0.074-0.091 mmol/min/m^2 (Table 1). Tubular reabsorption of calcium during pregnancy was high and ranged between 97.79 and 99.23% (Table 1). In week 4 of single gestations, we observed a transient though significant decrease in Ca^{2+} reabsorption. As compared to the pre-gestational period, calcium urinal excretion in goats during week 8 of the single gestation group significantly ($P \leq 0.05$) decreased from 1.60 to 0.70 μmol/min/m^2 (Table 1). This reduced excretion level was upheld throughout the subsequent months of gestation and was, until the end of the experiment, nearly twice lower than that observed during both the pre-gestational period and in week 4 of gestation. In the goats with twin pregnancies, a decrease in calcium renal excretion, from 1.50 to 0.90 μmol/min/m^2 , was observed as early as in the first month of gestation; however, the changes did not prove statistically significant (Table 1). It was not until the 2nd month of gestation when changes in calcium excretion became significant. Calcium urinal excretion was subject to larger variation in the goats with twin pregnancy compared to those with a single foetus; however, the parameter was still much lower than that observed in the pre-gestational period.

Blood plasma inorganic phosphorus did not change significantly during the studied period in either group of goats (Table 2). In the single-pregnant goats it ranged between 1.57 and 1.82 mmol/l, while in the goats of the other group between 1.57 and 1.98 mmol/l. Inorganic phosphorus clearance over the first 8 weeks of single-foetus gestation remained relatively stable (Table 2). In week 12 of gestation, the clearance of this mineral significantly ($P \leq 0.01$) decreased and remained until the end of gestation (except for week 16) significantly lower than that observed during the pre-gestational period. In the goats with twin pregnancies, a significant reduction in the clearance was observed as soon as the 18th week of gestation. The values observed in weeks 8, 12, 16, and 20 of gestation were significantly lower than those measured in the pre-gestational period. In the last week before parturition, inorganic phosphorus renal clearance increased nearly two-fold. The value of this parameter was significantly ($P \leq 0.01$) higher compared to values observed in the same group at 8, 16, and 20 weeks of gestation, as well as in the respective periods in single-pregnancy goats (Table 2). The load of inorganic phosphorus filtered in the renal glomeruli to the primary urine did not vary significantly over gestation and in both goats groups remained within the range 0.082-0.110 mmol/min/m^2 (Table 2). Tubular reabsorption of P_{inorg} in goats with single pregnancies increased gradually during the first 3 months of gestation. The means ob-

Table 2

Inorganic phosphorus concentration in blood plasma (P) and clearance (C), glomerular filtration (F), tubular reabsorption (TR), and excretion with urine (UV) in single and twin pregnant goats

Week of pregnancy		P (mmol/l)		C (ml/min/m2)		F (mmol/min/m^2)		TR (%)		UV (mmol/min/m^2)	
		single pregnant	twin pregnant	single pregnant	twin pregnant	single pregnant	twin pregnant	single pregnant	twin pregnant	single pregnant	twin pregnant
0	$\bar{x}$	1.57	1.57	0.297 ^{D,F,G}	0.297^{C,D,E,F}	0.082	0.082	99.35 ^{d,f}	99.35^{C,D,e,f}	0.0005	0.0005
(*A*)	SD	0.28	0.28	0.182	0.182	0.022	0.022	0.50	0.50	0.0003	0.0003
4	$\bar{x}$	1.63	1.76	0.245	0.209	0.088	0.102	99.54	99.67	0.0004	0.0005
(*B*)	SD	0.41	0.27	0.055	0.111	0.025	0.010	0.16	0.15	0.0001	0.0004
8	$\bar{x}$	1.60	1.78	0.237	0.163 ^{A,G}	0.083	0.096	99.55	99.67 ^{A}	0.0004	0.0003
(*C*)	SD	0.29	0.36	0.096	0.038	0.020	0.025	0.16	0.17	0.0002	0.0001
12	$\bar{x}$	1.67	1.82	0.183 ^{A}	0.169 ^{A}	0.087	0.102	99.65 ^{a}	99.69 ^{A}	0.0003	0.0003
(*D*)	SD	0.39	0.47	0.056	0.071	0.028	0.036	0.13	0.20	0.0001	0.0002
16	$\bar{x}$	1.81	1.74	0.230	0.188 ^{A,G}	0.109	0.094	99.51	99.66 ^{a}	0.0004	0.0003
(*E*)	SD	0.45	0.48	0.082	0.052	0.111	0.028	0.33	0.10	0.0003	0.0001
20	$\bar{x}$	1.82	1.86	0.186 ^{A}	0.159 ^{A,G}	0.089	0.099	99.62 ^{a}	99.62 ^{a}	0.0003	0.0004
(*F*)	SD	0.31	0.52	0.068	0.049	0.028	0.023	0.16	0.33	0.0001	0.0004
21	$\bar{x}$	1.78	1.98	0.157 ^{A,**}	0.337^{C,E,F}	0.096	0.110	99.45	99.40	0.0003	0.0006
(*G*)	SD	0.22	0.60	0.050	0.225	0.026	0.037	0.67	0.42	0.0001	0.0007

$\bar{x}$ – mean, SD – standard deviation;
a, d, e, f – significance of differences ($P \leq 0.05$) of means in particular weeks of pregnancy;
A, B, C, D, E, F, G – significance of differences ($P \leq 0.01$) of means in particular weeks of pregnancy;
** significance of differences – ($P \leq 0.01$) of arithmetic means in particular weeks in single and twin pregnancies.

served in weeks 12 and 20 were significantly ($P \leq 0.05$) higher compared to those found in the pre-gestational period (Table 2). Phosphorus TR increased significantly during the 2nd month of twin gestation. At 4, 12, 16, and 20 weeks of twin gestation, this parameter reached, respectively, 99.67, 99.69, 99.66, and 99.62% of the filtered load and was significantly higher compared to the pre-gestational period. During the last, 21st week of gestation, the net reabsorption of phosphorus decreased to 99.40% and did not differ significantly from that observed in non-pregnant goats. Urinal excretion of inorganic phosphorus did not show significant changes over the entire studied period (Table 2) with values similar in both groups, ranging between 0.30 and 0.60 μmol/min/m^2.

Discussion

Blood plasma calcium concentration in pregnancy remained relatively stable in both groups of goats and did not exceed the reference values (WINNICKA 2004). In pregnant women and female rats, the plasma concentration of Ca^{2+} does not change with the development of gestation (KOVACS & KRONENBERG 1997; KALKKWARF *et al.* 1999; PRENTICE 2000; O'BRIEN *et al.* 2003). KOVACS and KRONENBERG (1997) report that a decrease in total calcium observed in women results from a lower concentration of albumins in the plasma. As a consequence, the concentration of protein-bound calcium fraction decreases, while the concentration of ionised calcium remains unchanged. In pregnant rats, on the other hand, a reduction of total plasma calcium results from a decrease in both forms of calcium (ELZEN *et al.* 1995). Presumably, neither fraction of calcium changes in pregnant goats. In small ruminants, plasma levels of albumins do not seem to vary significantly during pregnancy. BRZOSTOWSKI *et al.* (1995) and EL-SHERIF and ASSAD (2001) report that plasma concentration of albumins in pregnant ewes does not decrease, also supported by our data for pregnant goats (JANKOWIAK *et al.* 2006).

Adaptive changes in the management of calcium and phosphorus occur in the female as soon as gestation begins, long before the period of the highest demand of the foetus for the elements (GARNER *et al.* 1988; DE ROUFFIGNAC & QUAMME 1994; DAI *et al.* 2001). The changes involve the metabolism of osseous tissue, intestinal absorption, and urinal excretion. In pregnant women, UV_{Ca} increases nearly twofold; consequently, the kidney causes calcium loss instead of retaining the mineral in the organism. According to KOVACS and KRONENBERG (1997), an increased level of urinal excretion of calcium during pregnancy results from the amount of glomerular filtration and meal-induced hypercalcaemia (elevated blood plasma level of ionised calcium after a meal, due to enhanced intestinal absorption). In the studied goats, glomerular filtration did not alter calcium levels (MICHAŁEK *et al.* 2008), which with a slight increase in calcium tubular reabsorption resulted in a significant reduction in urinal excretion of this mineral. Also, no effect similar to food-induced hypercalcaemia has been observed in ruminants. The constant filling of the proventriculus and a permanent supply of chyme into the small intestine imply that only a small quantity of the absorbed calcium depends on the time of feeding, thus an effect of periodical food-induced increase in plasma calcium virtually does not exist in ruminants (SAREŁO *et al.* 2003).

In a newborn child, 98% of total calcium and 80% of total phosphorus is contained in the osseous tissue (PRENTICE 2000). The requirements of the foetus for these minerals increases significantly in the second half of gestation and reaches its peak in humans during the 3rd trimester (KOVACS & KRONENBERG 1997; PRENTICE 2003). There is 11.5 g of calcium and 6.6 g of phosphorus on average in the body of a newborn kid. These quantities mean that 90 g of calcium and 25-50 g of phosphorus have been transferred through the placenta. An average daily requirement of a pregnant goat during the last 6 weeks of gestation is 1-2 g and 0.6-1.2 g for calcium and phosphorus, respectively (PFEFFER & RODEHUTSCORD 1998; MESCHY 2002). A decrease in urinal excretion of calcium in goats during pregnancy does not seem to have a significant effect in terms of the needs related to the development and mineralisation of the skeletal system of the foetus. An analysis of the results has revealed that a reduction of Ca excretion from 1.50 to 0.70 μmol/min/m^2 allows saving less than 10 mg of calcium per day, whereas the daily requirement of the foetus in the second half of gestation exceeds 150 mg (PRENTICE 2003). The results presented in this study imply that increased enteric absorption of Ca and reabsorption of the osseous tissue represent the main factors in a pregnant doe's organism that guarantee the appropriate supply of calcium necessary for both mineralisation of the foetus's osseous tissue and maintenance of proper blood plasma levels of this element. A small proportion of renal excretion in the system's general management of this element under physiological conditions is confirmed by, among others, low differences in calcium tubular reabsorption and excretion observed between single- and twin pregnant goats. Ca requirements of the latter group of goats during the second half of gestation, resulting from the necessity to provide optimum developmental conditions for the skeletons of two foetuses, must undoubtedly be much higher. In a woman pregnant with twins, as compared to a single pregnancy, plasma concentration of calcitriol, osseous issue reabsorption markers, and PTHrP are much higher (PRENTICE 2000; O'BRIEN *et al.* 2003). The foetus and the placenta are the main sources of PTHrP; the total quantity of the peptide must increase, since it is synthesised by two foetuses and a higher placental tissue mass (PRENTICE 2003).

The concentrations of inorganic phosphorus did not differ between the non-pregnant gats and both groups of pregnant does over the entire period of gestation. It should be emphasized that during the entire study period, plasma P_{inorg} concentrations remained near the lower limit of the reference range (WINNICKA 2004). Data from the literature are quite divergent in relation to changes in inorganic phosphorus levels during pregnancy in both women and animals. Some authors have found no changes (HUSAIN & MUGHAL 1992; BRZOSTOWSKI *et al.* 1995; PRENTICE 2003; SAREŁO et al. 2003), while others report an increase or a decrease in the concentration of this element (REITZ *et al.* 1981; MICHAŁEK *et al.* 2008). Maintaining the phosphate steady state is a more complex task if compared with calcium management. Inorganic phosphorus in the blood plasma is in equilibrium not only with that found in the osseous tissue, but also with that incorporated in a number of organic compounds (AHMED *et al.* 2000).

With a sufficient supply of phosphorus with food and with its proper concentration in the blood plasma, the kidneys excrete with final urine approx. 10-15% of the load of P_{inorg} filtered to the primary urine (BONJOUR & CAVERZASIO 1984). However, under deficiency of phosphorus provision and low plasma concentrations, the mineral may be reabsorbed in nearly 100% (BONJOUR & CAVERZASIO 1984). In the studied goats, the tubular reabsorption of inorganic phosphorus was very high over the entire period of the experiment and reached more than 99.3%. Less than 0.7% of the phosphorus contained in the primary urine was excreted with the final urine. The high phosphorus reabsorption rate, as well as plasma concentration only slightly above the lower physiological limit, may indicate a shortage of this element in the diet. As from 10-12 weeks of gestation, urinal excretion of phosphorus in pregnant women is nearly twice at that observed in non-pregnant women. As for calcium, the enhanced glomerular filtration rate is a significant factor in this increase (PRENTICE

2003). Apart from the last week of gestation, renal excretion of phosphorus was lower compared to that of non-pregnant animals. This was influenced by a lack of increase in glomerular filtration and a significant increase in tubular reabsorption from the 3rd month of gestation, in the single-pregnant goats, and from the 2nd month in the twin-pregnant does. The observed increase in renal retention of inorganic phosphorus could, however, secure the needs of the growing foetus (foetuses) only to a small extent, particularly in the latter half of gestation. The results presented indicate that the processes related to osseous tissue metabolism, probably controlled by PTHrP, play the key role in the maintenance of a relatively stable level of inorganic phosphorus in the blood plasma of pregnant goats and in provision of P_{inorg} to the foetuses in a proper amount (KOVACS & KRONENBERG 1997).

In summary it should be stated that the kidneys efficiently regulate the calcium-phosphate balance in both single- and twin- pregnant goats. Despite the observed differences in the values of the studied parameters of renal function, plasma concentrations of calcium and inorganic phosphorus in subsequent weeks of gestation remained within the reference limits. We have not found any clear-cut differences in the renal function of single- and twin- pregnant goats. It seems that enteric absorption and osseous tissue metabolism are equally important for the maintenance of the appropriate calcium-phosphate state.

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