Hypocalcemia and Pregnancy-Induced Hypertension Produced By Maternal Fasting

Jorge A. Prada, Richardus Ross, and Kenneth E. Clark

During pregnancy, maternal calcium needs increase as a result of increasing calcium requirements for fetal bone development. These needs have to be completely supplied by the mother via placental transfer. Several studies link low serum ionized calcium concentrations with the development of hypertension and pregnancy-induced hypertension. We hypothesized that maternal hypocalcemia would develop concomitantly with the development of hypertension in sheep that were fasted in late gestation. Sixteen instrumented ewes were used in the present study. After a 2-day baseline period, food was withdrawn from 10 animals in the experimental group (group 2) for 3 days, whereas the remaining six were allowed to eat and drink normally (group 1). Blood pressure, uteroplacental blood flow, and heart rate were monitored daily. Fasted animals were given deionized water (calcium free) to drink, whereas control animals were given tap water containing 32.9 mg/l calcium concentration. Based on the analysis of the ionized calcium concentration response to fasting, group 2 animals were placed in one of two groups: hypocalcemia did not develop in group 2a, whereas in group 2b the ionized calcium concentration decreased 27% (from 1.09±0.07 to 0.80±0.06 mM, p=0.01) by the third day of fasting. Group 2b responded with a 16% elevation in maternal blood pressure (p=0.01) and a 43% reduction in uteroplacental blood flow. Furthermore, a positive correlation was found between maternal and fetal blood ionized calcium concentrations (r=0.860). The intravenous infusion of calcium gluconate to the animals in group 2b resulted in a significant (p=0.05) recovery of blood ionized calcium concentration, reduction of blood pressure, and recovery of uteroplacental blood flow. The results of the present study are interpreted to suggest that altered calcium concentrations during the last trimester of multiple ovine pregnancy may play an important role in the development of pregnancy-induced hypertension. (Hypertension 1992;20:620–626)

KEY WORDS • hypocalcemia • fasting • sheep • hypertension, pregnancy-induced

Numerous explanations have been proposed to account for the development of pregnancy-induced hypertension, including incompatibilities between the maternal and fetal blood types, high salt (NaCl) intake, calcium deficiency, poor general nutrition, changes in the renin-angiotensin system, and a predisposed genetic make-up.1-7 In humans, pregnancy-induced hypertension is a hypertensive disorder peculiar to pregnancy that usually develops between the 30th week of pregnancy and the end of the first week postpartum. If associated with albuminuria, edema, or both, the disorder is termed preeclampsia.1-7 The etiology of pregnancy-induced hypertension is still unknown: it develops in 10–15% of pregnant women and characteristically occurs in young primigravidas2 and women with preexisting hypertension or vascular disease.10

Several recent studies have linked hypocalcemia and high blood pressure.11-14 Pregnancy constitutes a major challenge for calcium homeostasis because calcium is actively transported from mother to fetus across the placenta. The fetus requires a considerable amount of calcium for skeletal development during the last trimester of pregnancy. The fetal calcium requirements increase sharply at approximately the 30th week in the human fetus. By term, the fetus has accumulated as much as 28 g calcium, 80% of this during the third trimester.15-17 Thatcher and Keith18 have reported that fasting pregnant sheep for 3 days resulted in a significant elevation in blood pressure, as well as proteinuria, ketonuria, decreased glomerular filtration rate, decreased cardiac output, and decreased uteroplacental blood flow (UBF). We hypothesized that hypocalcemia in fasted pregnant sheep would be associated with maternal hypertension. The present study was therefore designed to investigate the effects of 3 days of fasting on maternal blood ionized calcium concentration [Ca2+], mean arterial blood pressure (MBP), and UBF in pregnant sheep and to evaluate the effects of these changes on parameters of fetal well-being such as blood pressure, heart rate, [Ca2+], and oxygenation.

Methods

Animal Preparation

Sixteen pregnant ewes of mixed breed were obtained from Morris & Co., Reistertown, Md. Animals (110–115 days of gestation and weighing between 50 and 60 kg) were sedated with diazepam (10 mg i.v.) (Valium,
Hoffmann-La Roche Inc., Nutley, N.J.) and then anesthetized with sodium pentobarbital (15 mg/kg) (Steris Laboratories, Phoenix, Ariz.) before receiving a hyperbaric spinal anesthetic (15 mg) (1% tetracaine hydrochloride, Winthrop Pharmaceuticals, New York). Supplemental doses of sodium pentobarbital were administered as needed for maintenance of anesthesia. Animals were secured in the supine position and draped aseptically. The maternal femoral artery and vein were isolated and cannulated with polyvinyl catheters that were advanced to the level of the distal aorta and inferior vena cava, respectively. Electromagnetic flow probes (Dieno, Los Angeles, Calif.) of appropriate size were placed on the left and right middle uterine arteries through a 15-cm sterile, lower abdominal incision to subsequently monitor blood flow to the uterus. After hysterotomy, polyvinyl catheters were inserted into the fetal femoral artery and vein. Catheters and flow probes were exteriorized through the midline incision, passed subcutaneously to the ewe's left flank, placed in a cloth pouch, and secured to the ewe's side.

Antibiotics (6 cc i.m.) (Combicotics, G.C. Hanford Manufacturing Co., Syracuse, N.Y.) were administered on the day of surgery and 3 days after surgery. All animals were housed in individual portable stainless steel cages and provided with standard laboratory diets (Rumilab, Purina Ralston, St. Louis, Mo.) and water ad libitum. Animals were allowed an adequate recovery period before fasting. Animals were not exposed to any experiments preceding the fasting study.

Maternal catheters were flushed daily with heparin sodium (1,000 USP units/ml) (Elkins-Sinn Inc., Cherry Hill, N.J.) and fetal catheters with heparin (500 USP units/ml) to maintain patency. All surgical and experimental procedures were performed in accordance with the Institutional Animal Care and Use Committee guidelines of the University of Cincinnati. 

Maternal and Fetal Measurements

Maternal and fetal systemic arterial blood pressures were measured via the appropriate catheter using a model MP-15 blood pressure transducer (Micron Instruments, Los Angeles, Calif.) anchored at the level of the maternal and fetal sterna. Fetal blood pressures were corrected for amniotic fluid pressure. Heart rates were determined with a cardiotachometer (SensorMedics Instruments, Fullerton, Calif.) triggered by the arterial pressure pulse. UBF was measured by an electromagnetic flowmeter (model RF-1000, Dienco, Los Angeles, Calif.). Electromagnetic flow probes (Dieno) were calibrated with saline and were linear over the flow rates measured. Blood pressure, heart rate, and UBF were recorded continuously for 60 minutes twice daily on a pen-writing dynograph physiological recorder (model R612, SensorMedics).

Maternal and fetal arterial blood samples were collected anaerobically into heparinized syringes. Arterial blood gas values (pH, PaO2, and PaCO2) were immediately determined with a blood gas analyzer (model BMS3 MK2 Micro System, Radiometer, Copenhagen, Denmark), operating at 39°C. Oxygen content was determined using model LEX-O2 CON TL oxygen content analyzer (Cavitron, Waltham, Mass.). Maternal and fetal blood glucose concentrations were determined with a glucose analyzer (model 27, Yellow Springs Instrument Co., Yellow Springs, Ohio). Samples for blood [Ca2+] were collected anaerobically in nonheparinized syringes and immediately determined by use of an ionized calcium analyzer (model ICA1, Radiometer). Blood [Ca2+] was adjusted to pH 7.4.

Experimental Protocol

Ten ewes in late gestation (121±2 days of gestation) with either singleton or multiple fetuses (two singletons, seven twins, and one triplet) were used to study the effects of fasting. The blood pressure and heart rate of the mother and fetus were measured daily in the morning and afternoon for 60 minutes for a period of 5 days. Blood samples were taken daily in the morning to determine maternal and fetal blood [Ca2+] and glucose concentrations, arterial PaO2, PaCO2, pH, hematocrit, and O2 content. Tap water and food were provided ad libitum between 9 AM and 5 PM for the first 2 days. Food was then withdrawn, and deionized (calcium free) water was provided for the next 3 days. At the end of the 3-day fast, an intravenous administration of calcium gluconate (Invenex, Melrose Park, Ill.) at the rate of 0.465 meq/min was slowly infused for 20 minutes into four of the five animals that became hypocalcemic. The effects of the calcium infusion on blood [Ca2+], MBP, and UBF were determined at 60 minutes after the end of the infusion.

Identical measurements were made over a period of 5 days in a control group of six instrumented pregnant ewes provided with standard laboratory diets and tap water. Additionally four animals received an intravenous infusion of calcium gluconate.

Calculations, Statistical Analysis

In each animal, the mean value (n=4) for each sample parameter for the 2 days before fasting (morning and afternoon) served as the baseline value for that animal. Similarly, daily morning and afternoon values were calculated as the mean±SEM for each of the 3 experimental days. For statistical analyses, fasted animals (group 2) were subdivided according to the direction and degree of the blood [Ca2+], response by the third day of fasting. For example, an animal was considered hypocalcemic and was assigned to group 2b if the ionized calcium concentration by the third day of fasting had decreased below two standard deviations from its prefasting baseline value. Allfasted animals which did not meet this criterion were considered to be normocalcemic and were assigned to group 2a. All results are expressed as mean±SEM. Cardiovascular and biochemical responses of the two fasted groups were compared with each other and with the control group (group 1) by analysis of variance. The statistical significance of differences between means was tested by Newman-Keuls test, and a value of p≤0.05 was considered significant. Cardiovascular and biochemical responses to calcium gluconate infusions (before and after) were analyzed using Student's t test, and a value of p≤0.05 was considered significant.

Results

Maternal Changes

Group 1 (n=six twins). As shown in Table 1, control animals demonstrated no significant changes in blood
ionized calcium concentration, MBP, UBF, or heart rate. Blood gas status (data not shown) also demonstrated no change during the 5-day period.

**Group 2a (n=5, two singletons and three twins).** As shown in Figure 1 and Table 2, there were no significant changes in [Ca$^{2+}$], MBP, or UBF during the 3 days of fasting when compared with the baseline parameters. However, there was a significant (p=0.05) 20% decrease in heart rate by the third day of fasting when compared with the baseline value. Additionally, there was a significant (p=0.01) decrease of 50% in plasma glucose concentration as a result of fasting. PaO$_2$, PaO$_2$, pH, and O$_2$ content did not change in this group during the experimental period (data not shown).

**Group 2b (n=5, four twins and one triplet).** In contrast to group 2a animals, there was a significant 27% decrease (from 1.09±0.07 to 0.80±0.06 mM, p=0.01) in the blood ionized calcium concentration during fasting (Figure 1). Group 2b animals also demonstrated a significant (p=0.01) 16% increase in MBP (from 83±4 to 96±4 mm Hg) (Table 3). A significant (p=0.009) negative correlation was found between maternal ionized calcium concentration and MBP (r=-0.560, Figure 2). Plasma glucose concentrations showed a significant (p=0.01) 41% decrease similar to those of group 2a, declining by the second day of fasting (Table 3). UBF decreased significantly during fasting, falling from 1,073±132 to 608±192 ml/min (Figure 3). In one animal, the decrease in UBF was more dramatic. UBF fell from 950 to 157 ml/min. Uterine vascular resistance showed a significant (p=0.01) increase. By the third day of fasting, vascular resistance increased from 0.083±0.014 to 0.250±0.082 mm Hg · ml$^{-1}$ · min$^{-1}$. A high correlation (r=0.526, p=0.009) was found between [Ca$^{2+}$] and UBF (Figure 4). Neither heart rate nor blood gas values (data not shown) changed significantly from baseline values.

**Fetal Changes**

The mean fetal blood [Ca$^{2+}$], (1.29±0.03 mM) during the baseline period (groups 2a and 2b pooled) was significantly higher than the mean maternal blood [Ca$^{2+}$], of 1.09±0.04 mM (p=0.05). Fetal blood glucose concentration decreased significantly (p=0.05) in groups 2a and 2b as a result of maternal fasting (Tables 2 and 3). As shown in Figure 5, there was a significant (p=0.003) positive correlation between maternal and fetal blood glucose (r=0.532).

In group 2a pregnancies, fetuses demonstrated no significant changes in fetal blood [Ca$^{2+}$] during maternal fasting when compared with the baseline period (1.29±0.06 to 1.22±0.02 mM, Figure 6). Furthermore, no changes in fetal MBP, heart rate, pH, PaO$_2$, PaO$_2$, or O$_2$ occurred during the experimental period of 3 days as compared with baseline (Table 2).

In group 2b pregnancies, the fetal MBP remained constant (Table 3) despite maternal hypertension, but fetuses became hypocalcemic (1.30±0.04 to 1.06±0.07 mM, p=0.01, Figure 6) concomitantly with the development of maternal hypocalcemia. A highly significant (p=0.0001) positive correlation was found between maternal and fetal blood [Ca$^{2+}$], (r=0.860, Figure 7). Although, PaO$_2$, and O$_2$ content decreased with the decrease in UBF, this did not reach significance. There were no significant changes in fetal hematocrit (data not shown). However, as mentioned earlier the mean fetal blood glucose concentration decreased significantly from 15.2±2.1 to 10.3±1.5 mg% (p=0.05, Table 3).
TABLE 2. Maternal and Fetal Cardiovascular and Blood Gas Values for Group 2a (Normocalcemic)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Maternal</th>
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<td></td>
<td>Baseline</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
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<tr>
<td>MBP (mm Hg)</td>
<td>81±3</td>
<td>76±3</td>
<td>75±3</td>
<td>75±3</td>
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<td>Heart rate (bpm)</td>
<td>102±4</td>
<td>95±11</td>
<td>86±10</td>
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<td>UBF (ml/min)</td>
<td>982±121</td>
<td>1,025±89</td>
<td>937±78</td>
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<td>Glucose (mg%)</td>
<td>67.2±4.2</td>
<td>49.6±3.3*</td>
<td>35.5±0.5*</td>
<td>33.7±3.8*</td>
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<tr>
<td>Fetal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>45±3</td>
<td>42±4</td>
<td>42±4</td>
<td>42±2</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>167±5</td>
<td>156±6</td>
<td>152±4</td>
<td>163±9</td>
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<td>pH</td>
<td>7.384±0.007</td>
<td>7.390±0.015</td>
<td>7.391±0.007</td>
<td>7.398±0.014</td>
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<td>Pao2 (mm Hg)</td>
<td>20.0±0.6</td>
<td>21.8±1.4</td>
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<td>PacO2 (mm Hg)</td>
<td>37.3±2.0</td>
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<td>O2 content (vol %)</td>
<td>6.9±0.5</td>
<td>6.8±0.5</td>
<td>7.3±0.4</td>
<td>6.8±0.7</td>
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<tr>
<td>Glucose (mg%)</td>
<td>20.5±0.7</td>
<td>13.6±0.8*</td>
<td>10.5±0.8*</td>
<td>10.0±0.7*</td>
</tr>
</tbody>
</table>

MBP, mean blood pressure; bpm, beats per minute; and UBF, uteroplacental blood flow. Values are mean±SEM; n=5.

Table 2. Maternal and Fetal Cardiovascular and Blood Gas Values for Group 2a (Normocalcemic)

Administration of Calcium Gluconate to Control Group and Group 2b

Maternal changes. The intravenous infusion of calcium gluconate (0.465 meq/min for 20 minutes) to an additional four animals in the control group resulted in no significant changes in MBP or UBF despite a significant increase in blood [Ca2+], (from 1.03±0.05 to 1.19±0.06 mM, p=0.05).

Group 2b. The intravenous infusion of calcium gluconate to four of the five ewes in group 2b returned the maternal blood [Ca2+] toward baseline concentrations (0.80±0.06 to 1.04±0.09 mM, p=0.01, Table 4) within an hour. In contrast to animals in the control group, MBP decreased progressively during the 60 minutes after the calcium gluconate infusion (from 96±4 to 85±5 mmHg, p=0.01, Table 4). Amelioration of the effect of fasting on the [Ca2+] was effective in restoring UBF toward prefasting values in only three of the four animals (p=0.001, Table 4). In contrast, the dramatic fall in UBF that accompanied fasting in the fourth animal was not reversed by the infusion of calcium gluconate, and UBF continued to fall (Table 4).

TABLE 3. Maternal and Fetal Cardiovascular and Blood Gas Values for Group 2b (Hypocalcemik)

<table>
<thead>
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<th>Parameters</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>83±4</td>
<td>85±5</td>
<td>82±7</td>
<td>96±4*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>107±7</td>
<td>93±4</td>
<td>97±4</td>
<td>99±8</td>
</tr>
<tr>
<td>UBF (ml/min)</td>
<td>1,073±132</td>
<td>1,058±163</td>
<td>806±201</td>
<td>608±192*</td>
</tr>
<tr>
<td>Glucose (mg%)</td>
<td>68.4±3.7</td>
<td>48.7±2.4*</td>
<td>40.4±2.4*</td>
<td>50.3±3.8*</td>
</tr>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>40±2</td>
<td>39±3</td>
<td>38±3</td>
<td>41±3</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>179±6</td>
<td>166±3</td>
<td>168±4</td>
<td>163±7*</td>
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<tr>
<td>pH</td>
<td>7.395±0.009</td>
<td>7.387±0.017</td>
<td>7.378±0.020</td>
<td>7.373±0.021</td>
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<tr>
<td>Pao2 (mm Hg)</td>
<td>21.4±1.4</td>
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<td>PacO2 (mm Hg)</td>
<td>35.7±1.3</td>
<td>34.1±1.2</td>
<td>34.6±2.1</td>
<td>32.5±2.1</td>
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<tr>
<td>O2 content (vol %)</td>
<td>6.0±0.7</td>
<td>6.0±0.6</td>
<td>5.5±0.9</td>
<td>4.7±1.1</td>
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<tr>
<td>Glucose (mg%)</td>
<td>15.2±2.1</td>
<td>12.7±1.8</td>
<td>9.0±1.8*</td>
<td>10.3±1.5*</td>
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</tbody>
</table>

MBP, mean blood pressure; bpm, beats per minute; and UBF, uteroplacental blood flow. Values are mean±SEM; n=5.

Fetal changes. The mean fetal blood [Ca2+] in group 2b increased (from 1.06±0.07 to 1.23±0.01 mM, p=0.01, Table 4) over the subsequent hour in response to the intravenous infusion of calcium gluconate to the ewes in group 2b. There were no corresponding effects on fetal MBP, heart rate, Pao2, PacO2, or O2 content. The infusion of calcium gluconate to the ewes in group 2b did not reverse the decline in fetal pH (Table 4).

Discussion

The existence of a link between calcium and hypertension has been postulated by several investigators. For example, it has been suggested that a lack of dietary calcium is associated with elevated blood pressure in adults. In a study by McCarron, hypertensive patients were found to consume significantly less calcium. It has further been reported that poor urban and rural Guatemalan women with a diet low in calories, proteins, and vitamins, but high in calcium have demonstrated one of the lowest rates of pregnancy-induced hypertension in the world.
Calcium exists in the blood in three forms, with a total normal concentration of 2.25-2.75 mM. Under normal conditions, 40% is present as a nondiffusible complex with protein; 5% is present as a diffusible but undissociated complex with citrate, bicarbonate, and phosphate; and 55% is present as free \([Ca^{2+}]\). Calcium homeostasis results from the integrated actions of parathyroid hormone (PTH), 1,25-dihydroxy \([1,25-(OH)_2] Vitamin D\), and calcitonin.\(^{21,22}\) PTH, which is released in response to a decrease in serum ionized calcium concentration, stimulates osteoclastic bone resorption to liberate calcium from bone into the blood. As the concentration of calcium in the blood rises, PTH activity is decreased and the rate of bone resorption decreases. PTH also stimulates the renal synthesis of 1,25-(OH)\(_2\) Vitamin D, which stimulates transepithelial absorption of both calcium and phosphate.\(^{23}\)

The influence of calcium on blood pressure is complex. It is proposed that when \([Ca^{2+}]\) is elevated in vascular smooth muscle cells, these cells become abnormally contracted, increasing the vascular resistance and blood pressure. To lower the blood pressure, \([Ca^{2+}]\) must be reduced. Increasing the blood \([Ca^{2+}]\) decreases the \([Ca^{2+}]\), by calcium-regulated mechanisms and produces relaxation of the vascular cell,\(^{24}\) and as a consequence the blood pressure decreases. High \([Ca^{2+}]\) in blood acts in the same manner as calcium channel blockers, preventing calcium from entering the cell, thus leading to relaxation.

The present study demonstrated that when pregnant sheep carrying twin or triplet pregnancies were fasted and given deionized water for 3 days, hypocalcemia and elevated arterial blood pressure occurred in 50% of the experimental animals. The hypocalcemia and elevated blood pressure were associated with reduced UBF, increased uterine vascular resistance, and decreased fetal blood glucose concentration and \([Ca^{2+}]\). Also, the present study clearly shows that fetal \([Ca^{2+}]\) is significantly higher than maternal \([Ca^{2+}]\), suggesting an active transport of calcium across the placenta. However, a fall in maternal calcium concentration was consistent with a fall in fetal calcium concentration, suggesting a reduced placental calcium transfer by an unknown mechanism. Nevertheless, a similar phenomenon was reported by Mughal et al\(^{25}\) in intrauterine growth retarded (IUGR)-perfused rat placentas. They found that the maternal-fetal clearance of \(^{45}\)Ca across IUGR placentas was significantly lower than control placentas.

Of the 10 sheep fasted, only five became hypertensive, with a significant reduction in blood calcium concentra-
tion and UBF. The sheep in which hypertension developed showed significant reduction in blood \([\text{Ca}^{2+}]\), whereas those which remained normotensive showed no significant changes in blood \([\text{Ca}^{2+}]\). The finding that groups 2a and 2b both showed similar and significant decreases in maternal plasma glucose concentrations, but only group 2b developed hypocalemia and hypertension, diminished the likelihood that the hypertension in group 2b was the result of low plasma glucose concentration. The possibility that the present experimental protocol may have altered other elements or electrolyte concentrations that could have effects on the parameters studied cannot be ruled out. However, further support for the role of calcium in modulation of the observed hypertension is provided by its reversibility after administration of calcium gluconate.

Previously, Morriss et al.26 have reported the effect of calcium on maternal and fetal cardiovascular parameters. In those studies, the sheep in which hypertension developed showed significant increase in blood pressure and significant decrease in uteroplacental blood flow; and \(\text{Ci} \, _1\), ionized calcium at pH=7.4.

The present study, the maternal ability to maintain adequate blood calcium concentration seems to be the determining factor in preventing hypertension, which may be accomplished by the integrated actions of PTH, 1,25-(OH)\(_2\) Vitamin D, and calcitonin. Also of importance may be the maternal parity, maternal storage of calcium, and maternal and fetal metabolic calcium requirements.

UBF declined 43%, confirming the decrease in UBF reported by other investigators in similar experimental conditions.18 The effects of UBF reduction have been an area of concern because of the risk of fetal and neonatal morbidity and mortality. The literature abounds with studies devoted to the investigation of many different factors concerning UBF and IUGR. The decreased UBF and the decreased \(\text{PaO}_2\) and \(\text{O}_2\) content we observed could have serious effects on the fetus if maintained on a chronic basis. In addition to hypocalemia, hypertension, and reduced UBF, we found a much higher incidence of premature labor (unpublished observation), a finding that has also been reported in humans20 after acute starvation.

It is well known that pregnancy-induced hypertension is common in multiple pregnancies.30 Based on our observations from the present study, this phenomenon might be explained as follows: the fetal content of calcium is related to fetal weight in a linear manner, with most of the accretion occurring late in pregnancy. The placenta also doubles its calcium content over the last 4 weeks of pregnancy. In ewes, placental transfer of calcium is increased in late twin gestation, day 122 (1.76 g/day) to day 140 (2.60 g/day).31 It seems reasonable to suggest that maternal, fetal, and placental calcium...
requirements could be readily met from maternal stores; however, in a situation where calcium intake is seriously decreased, this could cause undue disturbances to maternal and fetal calcium homeostasis.

The results of the present study identify hypocalcemia as a strong candidate as a mediator of ovine hypertension in pregnancy during fasting. The finding that maternal hypocalcemia and hypertension have significant detrimental effects on fetal calcium concentration warrants further detailed study of the relations between diet, intensity of pregnancy, and fetal well-being.

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