

# Prevention of Toxemia of Pregnancy in Ecuadorian Andean Women: Experience with Dietary Calcium Supplementation<sup>1</sup>

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*Pregnancy-induced hypertension (PIH) is a significant cause of low birth weight and maternal and neonatal death around the world. This article reviews work indicating that dietary calcium supplementation can sharply reduce the PIH incidence among pregnant women whose regular diet is calcium-poor. It also describes physiologic conditions prevailing during pregnancy that could explain calcium's major role in PIH—as well as supplemental calcium's great potential for preventing PIH among people with low-calcium diets.*

**T**oxemia of pregnancy or pregnancy-induced hypertension (PIH) is a disease that affects approximately 10% of all pregnancies around the world.<sup>3</sup> The problem tends to be especially acute in developing areas, where the incidence may go as high as 30% and where PIH is an important cause of maternal morbidity and mortality (1–3) as well as an important risk factor contributing to intra-

uterine growth retardation, prematurity, low birth weight, and neonatal death (4–6).

Despite PIH's public health significance, its etiopathologic mechanisms have still not been completely established (1). However, its association with certain maternal characteristics such as age, first pregnancy, residence at high altitudes, nutritional deficiencies, and lack of adequate prenatal care is well known (3). These various characteristics, all of which are common among our country's Andean population, could account for the high reported incidence of PIH in Ecuador and for its role as the country's leading cause of maternal death (7).

Historically, PIH has prompted a wide range of treatments, many of which have escaped adequate evaluation or have proven ineffective (3). Of course, generally speaking the best treatment for any disease is prevention, and in recent years some progress has been made toward preventing PIH. The present article reviews our experience with PIH prevention accomplished by providing calcium as a dietary supplement and suggests a possible physiologic mechanism that

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<sup>3</sup>The term "pregnancy-induced hypertension" (PIH) is used to distinguish between hypertension generated during pregnancy and that which merely coexists with pregnancy. PIH is divided into three categories (hypertension alone, preeclampsia, and eclampsia). The diagnosis of preeclampsia is based on development of hypertension (blood pressure  $\geq 140/90$  mmHg) plus proteinuria and edema. Eclampsia is typically characterized by these abnormalities plus PIH-induced convulsions.

could account for this measure's effectiveness.

## DIETARY CALCIUM INTAKE AND PIH

In 1980 Belizán and Villar suggested that a causal relationship existed between calcium intake and PIH. Their theory was based on observations made in Guatemala, where the study population exhibited a high intake of calcium associated with a low incidence of pre-eclampsia and eclampsia (8). Subsequent epidemiologic studies consistently demonstrated an inverse relationship between calcium intake and levels of arterial pressure in different populations (9, 10).

Along these lines, we previously reported (11) that pregnant women in Ecuador's Andean area consumed relatively low amounts of dietary calcium, barely 60% of that recommended by the World Health Organization (12). We found this deficiency to be particularly serious among pregnant adolescents, who constituted one-third of the sample studied and who experienced a significantly higher incidence of PIH than the rest of that sample. We also observed that pregnant women who developed PIH consumed 100 g less calcium per day, on the average, than those who remained normotensive. These results supported Belizán and Villar's hypothesis and suggested that insufficient calcium intake could constitute an additional risk factor for PIH in Ecuador's Andean population (8).

## TRIALS WITH DIETARY CALCIUM SUPPLEMENTS

As reported elsewhere (13, 14), we performed two controlled, randomized, double-blind clinical trials to explore the effect of dietary supplementation with calcium upon the incidence of PIH

among women with a dietary calcium deficiency.

In the first study (13), which included 106 young healthy primigravidas residing in Quito (2,800 meters above sea level), we found that administering 2 grams of elemental calcium per day from the twenty-fourth week of pregnancy to the day of delivery dramatically reduced PIH. That is, the PIH incidence was 27.9% among members of a placebo group but only 4.1% among those receiving the supplement (13). In addition, the average arterial pressure at the end of pregnancy was significantly lower in the group receiving the supplement (109/71 mmHg) than in the placebo group (119/75 mmHg).

The second clinical trial (14) included 56 primigravidas who were generally similar to those in the first trial, but who were considered at high risk of developing PIH because they yielded positive "roll-over test"<sup>4</sup> results (14). (We had previously reported that this test was useful in predicting PIH in Andean populations with a high incidence of the disease—15.) In this second study we again found that calcium supplementation sharply reduced the frequency of PIH, from 71% in the placebo group to 14% in the supplemented group; in addition, we confirmed that calcium supplementation was associated with a longer

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<sup>4</sup>The roll-over or supine pressor test protocol was as follows: All patients rested quietly in a seated upright position for 10 minutes after their arrival at the prenatal clinic. A baseline diastolic blood pressure was established by placing the subject in the left lateral recumbent position for 15 minutes, after which the blood pressure was measured twice and the mean of the two readings was recorded. The subject was then "rolled over" to the supine position, which was maintained for 5 minutes, after which the blood pressure was again measured twice and the mean of these two readings was recorded. The roll-over test results were considered positive if the average diastolic blood pressure (supine) showed an increase of 20 mmHg or more over the initial average (recumbent) pressure.

gestation period and higher infant birth weight.

Overall, these results confirmed previous reports indicating that calcium supplementation attenuates maternal arterial pressure in pregnancy, showing that it reduces the frequency of PIH among pregnant women with insufficient calcium intake (16, 17).

Therefore, in dealing with populations such as those studied (young primigravidas with low calcium intake residing at high altitudes), where high PIH incidences prevail along with high PIH-associated maternal and perinatal mortality, we suggest that providing supplemental calcium or ensuring an adequate dietary calcium intake during pregnancy offers a cheap and effective way of reducing the incidence of PIH, and that this treatment should be considered in preference to other proposed measures such as administration of low doses of aspirin (18).

## CALCIUM METABOLISM

### Normal Pregnancy versus PIH

Calcium metabolism undergoes a series of important adaptive processes during pregnancy that relate mainly to the active flow of calcium across the placenta to the fetus and that result in the transfer of approximately 30 grams, primarily to the fetal skeleton (19). In addition, the body's calcium balance is affected by expansion of the volume of extracellular fluid, which dilutes the calcium cations present, as well as by the physiologic hypercalciuria of pregnancy resulting from an increased rate of glomerular filtration (20).

Therefore, in order to maintain an appropriate calcium balance, a pregnant woman needs to assimilate more dietary calcium than one who is not pregnant.

(In this connection it is worth noting that the pregnant woman's plasma levels of 1,25-dihydroxyvitamin D<sub>3</sub>, possibly of placental origin, are increased during pregnancy to facilitate intestinal absorption of calcium—21, 22.) Accordingly, it has been recommended that a woman's calcium intake increase substantially during pregnancy to ensure that her greater need for the mineral is satisfied (23).

Most studies carried out to date have found that total serum calcium levels decrease in pregnancy, paralleling a decline in serum albumin concentrations (24). Although it has been reported that serum ionized calcium levels are lower or unaltered during pregnancy, it has also been suggested recently that the level of "true ionized calcium" (serum ionized calcium corrected for albumin concentrations) increases during normal pregnancy (25–27). These discrepancies may be explained by the fact that ionized calcium concentrations during pregnancy are related to dietary calcium intake; thus, as we have observed, women with a low calcium intake exhibit a significant decrease in ionized calcium serum levels during pregnancy, while women receiving calcium supplements have shown a significant increase (13).

These data suggest that the principal physiologic adaptations of calcium metabolism during pregnancy are directed at maintaining ionized calcium serum levels within narrow physiologic limits in the face of increased extracellular serum volume, increased urinary excretion, and transfer of calcium to the fetus. Hence, populations with a low dietary calcium intake have a critical need for calcium supplementation in order to ensure adequate availability of the mineral.

Regarding PIH, some authors have reported normal serum levels of ionized calcium in subjects with PIH, while others have observed significant reductions (28–31). PIH has also been associ-

ated with reduced excretion of calcium in the urine (32). Within this context, it is interesting that the first of our two aforementioned clinical trials found that the only two women who developed PIH despite taking calcium supplements showed no increase in the serum level of ionized calcium, while all 47 in this group who remained normotensive showed an increase in that parameter (13).

## Hemodynamic Changes

Important changes in cardiovascular and renal physiology occur during pregnancy. By the middle of gestation there are normally increases in cardiac output, blood volume, renal flow, and rate of glomerular filtration, together with decreases in blood pressure and peripheral vascular resistance (33). Cardiac output increases by 30% to 40% early in gestation (around 12 weeks), probably as a result of the peripheral vasodilation and reduced venous return observed in this period (34). Also, plasma volume increases by over 50%, an increase that begins in the first trimester and is maintained until the end of gestation (35).

Despite these increases in cardiac output and plasma volume, during a normal pregnancy blood pressure declines. This decline is apparent at the end of the first trimester and becomes most marked in the second trimester. Subsequently, arterial pressure begins a gradual rise that brings it to prepregnancy levels at the end of gestation (36).

The reasons for the decreased peripheral vascular resistance that plays a key role here remain unknown. However, it is presumed that this decreased resistance is related to an increase in the vascular production of vasodilators such as prostacyclin (37). Also, during normal pregnancy women are relatively refractory to the pressor effect of angiotensin II (38), and it has been postulated that vas-

cular sensitivity to this mediator can be restored by inhibitors of prostaglandin synthesis (39); however, this has not been consistently observed (40).

In PIH the hemodynamic changes that we have described do not occur. Instead one observes an increase in peripheral vascular resistance, failure to develop the physiologic hypervolemia of pregnancy, reduction in the rates of glomerular filtration and renal flow, and increased sensitivity to the pressor action of substances like angiotensin II (3). This increased sensitivity to the action of vasoconstrictors is one of the most important characteristics of PIH and is present months before the clinical manifestations of the disease appear (38). Thus, women who later develop PIH show increased sensitivity to angiotensin II, norepinephrine, and vasopressin as early as the fourteenth week of gestation, and this sensitivity becomes more evident as the pregnancy progresses (41).

It has been postulated that this increased sensitivity to vasoconstrictors is due to a reduction in the synthesis of vasodilating prostaglandins such as prostacyclin (42, 43). It has also been reported that in PIH there is a change in the balance between prostacyclin and thromboxane  $A_2$  in favor of the latter (44). However, if altered metabolism relating to thromboxane  $A_2$  and other derivatives of arachidonic acid were the primary cause of the disease, changes in the levels of prostacyclin and thromboxane should occur early in the pregnancy. The few published data on the quantification of eicosanoates (including thromboxane) in early pregnancy suggest that the balance between prostacyclin and thromboxane is not altered in this period. Moreover, Ylikorkala and colleagues (45) have reported that urinary excretion of prostacyclin was not reduced unless PIH was clinically evident. This suggests that altered eicosanoate metabolism may be im-

portant in the clinical manifestations of the disease but not in bringing about the primary change.

### **Suggested Role of Nitric Oxide**

We initially hypothesized that calcium supplementation could affect the vascular generation of prostacyclin to the extent that synthesis of this vasodilator is relatively dependent on extracellular calcium (46, 47). However, we recently determined that supplementation with 2 grams per day of elemental calcium in the second half of pregnancy does not increase production of prostacyclin by maternal-fetal vascular tissue (48). In view of this, we think it likely that the following conditions apply: Dietary calcium supplementation reduces the frequency of PIH by maintaining ionized calcium serum levels within narrow physiologic limits. In turn, those serum levels are crucial for production of nitric oxide (NO) derived from vascular endothelium, and this powerful vasodilator is responsible for maintaining the vasodilatation that characterizes normal pregnancy.

This hypothesis is based on the following points:

Vascular endothelium produces NO derived from L-arginine, which accounts for the biological actions of endothelium-derived relaxing factor (EDRF) (49, 50). It has been demonstrated that NO plays a fundamental role in controlling blood fluid and arterial pressure (51, 52), which has led to a theory that the cardiovascular system is in a state of vasodilatation maintained through basal generation of NO derived from L-arginine (53).

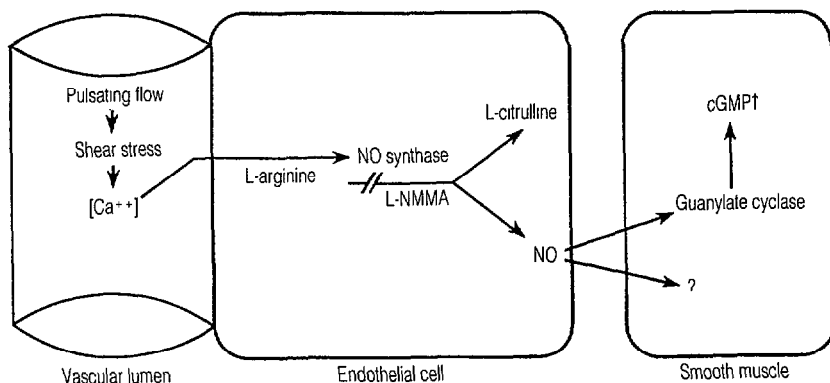
It has been demonstrated recently that the arteries of pregnant animals show increased EDRF activity compared to non-pregnant counterparts (54), and that the umbilical arteries of women with PIH show less generation of NO than those of women experiencing normal pregnancy

(A. Pinto, personal communication). Also, providing calcium supplementation to pregnant women has been shown to produce a significant drop in their vascular sensitivity to infusion of angiotensin II (55), and it is well known that EDRF plays an important role in controlling blood vessel reactivity (56).

Years ago it was demonstrated that EDRF liberation depends on the flow of ionized calcium across membranes (57), and the NO-synthase enzyme in the vascular endothelium was recently characterized as a calcium-dependent enzyme (58). Moreover, we have finally demonstrated that small variations in extracellular ionized calcium concentrations, similar to those observed in pregnant Andean women, profoundly affect formation of NO by the vascular endothelium (59). This latter work showed that the basal liberation of NO was at a maximum when the concentration of extracellular ionized calcium utilized to perfuse an aorta with intact endothelium was 1.25 mmol/l; when the calcium concentration was increased to 1.5 mmol/l or reduced to 1.0 mmol/l a significant drop in the basal liberation of NO was observed. We have also found that the liberation of NO induced by acetylcholine is dependent upon the concentration of extracellular ionized calcium (60).

Mechanical factors such as shear stress and pulsating flow, in the presence of physiologic concentrations of calcium, are the probable physiologic stimuli for liberation of NO (Figure 1). It has been shown recently that calcium can enter the endothelial cell through calcium channels that open in response to stretch (61). It is therefore likely that an increase in the basal liberation of NO during pregnancy occurs in response to an increase in plasma volume, which would be expected to increase the frictional forces that govern the influx of calcium into the cells and activation of the NO-synthase

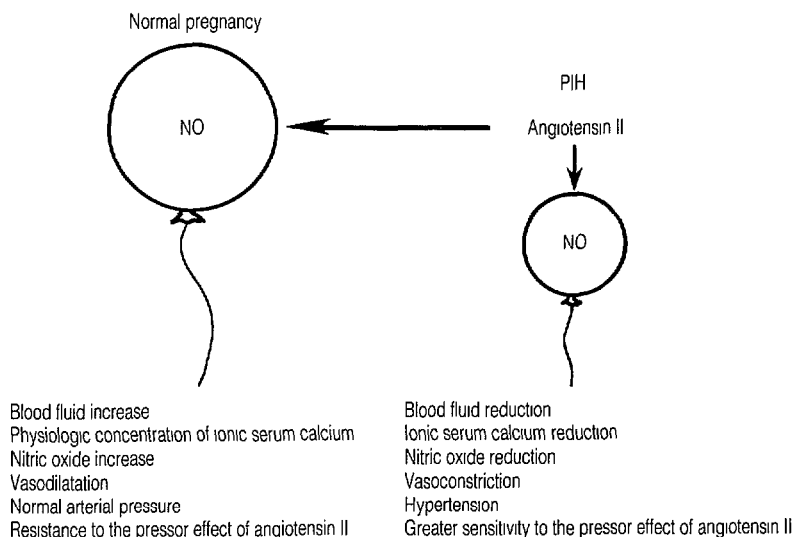
**Figure 1.** Proposed physiologic mechanism for liberation of nitric oxide (NO) derived from the vascular endothelium. The bloodstream's pulsating flow and resulting friction against the endothelial cells open channels for calcium, which activates the NO-synthase enzyme. This NO produced in the endothelium in turn activates the soluble enzyme guanylate cyclase and raises prevailing levels of cyclic guanosine monophosphate (cGMP), the agent that relaxes the vascular smooth muscle. The analog of L-arginine, N-monomethyl-L-arginine (L-NMMA), inhibits this synthesis.



enzyme (Figure 2). Indeed, it is conceivable that NO could be the unknown endogenous vasodilator responsible for reducing arterial pressure in patients with severe PIH who have been infused with

plasma volume expanders (62). In any case, it appears that any decrease in the ionized calcium serum levels necessary for these adaptive processes could be expected to favor development of PIH.

**Figure 2.** Participation of nitric oxide (NO) derived from vascular endothelium in hemodynamic adaptation during (a) normal pregnancy and (b) a pregnancy with PIH.



## CONCLUSIONS

This discussion of mechanisms aside, our results have demonstrated that dietary calcium supplementation during pregnancy is an economical and safe intervention that effectively reduces the frequency of PIH in young women with insufficient calcium intake.

The operational and financial difficulties inherent in establishing massive nutrition modification programs in countries such as Ecuador obviously need to be considered. However, the simple roll-over test can identify pregnant Andean women at high risk of developing PIH. Therefore, we are proposing that this test be incorporated into the clinical prenatal care routine of these Andean and similar populations, and that positive test results be followed by intervention with dietary calcium supplements.

It is recommended that such intervention be instituted in conjunction with a well-controlled protocol that permits confirmation of our initial clinical trial results. In addition, every effort should be made to ensure that those pregnant adolescents who are still undergoing skeletal growth have access to dietary sources of the calcium needed not only to meet the demands of their own growth, but also to promote proper evolution of their pregnancy and its successful outcome.

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