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Effect of Food Supplementation on Blood Pressure and on the Prevalence of Edema and Proteinuria during Pregnancy

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High incidence of elevated diastolic blood pressure (DBP) values and low frequency of lower limbs edema (LLE) have been commonly acknowledged as characteristics of pregnant women from low socio-economic strata in which protein-calorie malnutrition (PCM) is highly prevalent (Hytten and Leitch, 1971; Davis, 1971; Neutra, 1973). The purpose of this study was to explore the hypothesis that PCM is a determinant of high DBP and low incidence of LLE in these population groups.

Methods

Experimental design. The data presented here are drawn from a long-term prospective study on the effects of chronic malnutrition on physical growth and mental development (Klein *et al.,* 1973). The experimental design and the principal examinations made during the prenatal period and at birth have been described in detail in a previous publication (Lechtig *et al.,* 1975d). Two types of food supplement, "atole" and "fresco", are provided to the population of four rural Guatemalan villages. It should be stressed that the "fresco" contains no protein and provides only one third of the calories contained in an equal volume of "atole". In addition, both preparations have similar concentrations of the vitamins and minerals which are possibly limiting in the diets of these populations. Attendance to supplementation centers was voluntary, and a wide range of supplement intake during pregnancy was observed (Lechtig *et al.,* 1975d). In addition, all villages received preventive and curative medical care. A detailed description of the population has been presented elsewhere (Lechtig *et al.,* 1975d; Habicht *et al.,* 1974; Lechtig *et al.,* 1974).

Variables selected for the present analysis. The variables to be analyzed in the present article are shown in Table I. Data collection on these variables was standardized and the data collectors were systematically rotated among the four study villages.

The main dependent variables in the following analyses were both diastolic and systolic blood pressure (DBP and SBP, respectively), lower limbs edema (LLE) and proteinuria. Arterial pressure was determined by means of the mercurial manometer in the right arm, using an adult pressure gauge and with the patient in dorsal-decubitus position. SBP was defined as the pressure of the manometer when the first sound transmitted was heard; DBP was defined as the pressure of the manometer when the systolic tone of the pulse became weaker. Edema was defined as the

Table I
Main variables used in the present analysis

I. *Independent Variable:*
— Caloric supplementation during pregnancy

II. *Main Dependent Variables:*
— Diastolic Blood Pressure (DBP)
— Systolic Blood Pressure (SBP)
— Lower Limbs Edema (LLE)
— Proteinuria

III. *Potential Confounding Factors:*
A — Daily home diet at the end of the 2nd and 3rd trimester
B — Maternal anthropometry during pregnancy
— At any time of pregnancy: height and head circumference
— At the end of the first trimester of pregnancy: weight
C — Obstetrical history
— Parity, gestational age, birth interval, age of the mother and lactation during present pregnancy
D — Morbidity during pregnancy
— Composite indicator based on percent of time ill with anorexia, and/or cephalea and/or diarrhea
— Cord blood IgM levels
E — Socio-economic status (SES) of the family
— Composite indicator based on house, clothing and teaching

IV. *Information on the Newborn:*
— At birth: weight and sex

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presence of a persistent depression after applying pressure with the forefinger on the skin against two bony surfaces: the malleolus and the tibia. It was coded as follows:

0. Absent: when it was not detectable.
1. Malleolar: depression after applying pressure on the malleolar region.
2. Feet and legs: depression after applying pressure both in the malleoli as well as on the tibia.
3. Generalized: depression after applying pressure on different areas of the body, including the lumbosacral region.

The presence of LLE was defined by categories 1 or 2. Only one case belonging to category 3 was discarded from the present analysis.

Proteinuria was defined as the presence of abnormal quantities of proteins in the urine as detected by reagent tapes (Labstix, Ames Co., Elkhart, Indiana, U.S.A.) in a fresh urine sample (no more than 15 min. after emission), collected in the medical field unit of each village. A positive reaction (1+) was considered as presence of proteinuria because it indicated at least 30 mg percent of protein in the urine. It was coded as follows:

0. Absent: when the reaction was negative or "trace".
1. Present: when the reaction was positive, one or more crosses.

The main independent variable was ingestion of the supplement (the experimental treatment) during pregnancy. In addition, home intake was estimated through 24- and 72-hour recall surveys at the end of each trimester of pregnancy (Lechtig *et al.*, 1972). Both variables, supplement and home dietary intake, were expressed in terms of calories because analyses made during the last 4 years have shown that caloric intake during pregnancy is the main limiting factor in these populations (Lechtig *et al.*, 1975d). In consequence, the analyses presented below describe the entire study population without partitioning between the protein-calorie and the calorie supplementation villages. More detailed analyses on this subject will be provided to interested readers on request.

Maternal anthropometric examinations included height and head circumference as well as weight at the end of the first trimester of pregnancy (Lechtig *et al.*, 1976b). Lastly, the risk of intrauterine infection was gestational age, birth interval since the previous baby, age of the mother and duration of lactation during the present pregnancy (Lechtig *et al.*, 1975d). A composite morbidity indicator (ACD) of maternal morbidity during pregnancy was generated from data obtained through fortnightly interviews (Lechtig *et al.*, 1967b). Lastly, the risk of intrauterine infection was estimated by measuring IgM levels in cord blood (Lechtig *et al.*, 1974) and socio-economic status of the family was estimated through a composite scale (Lechtig *et al.*, 1975a). Weight of the newborn was determined within the first 24 hours of birth.

Table II
Completeness of data collection of the main variable of this study at the third trimester of pregnancy

	Total 1969-73
Number of births	651
Data:	
1. Ingestion of supplement	651
2. Blood pressure*	392 (60.2%)
3. Edema*	353 (54.2%)
4. Proteinuria**	199 (30.6%)

* Routine data collection started on June 1970.
** Routine data collection started on September 1972.

Table II presents the sample size for each of the variables during the 4 years of data collection (from January 1969 through February 1973) in the four villages. The figures correspond to the number of cases surveyed at the end of the third trimester of pregnancy. The lowest completion rates occurred in 1969 and 1970 because routine data collection was not instituted until June 1970.

Results

Tables III to VI provide the frequency distribution of SBP, DBP, LLE and proteinuria per trimester of pregnancy in the study population. In these Tables, each mother may have more than one measurement

Table III
Frequency distribution of systolic blood pressure (SBP) per trimester of pregnancy* in four rural Guatemalan villages

Categories of SBP (mm Hg)	Trimester of pregnancy: First (n=274) %	Second (n=364) %	Third (n=392) %
80-90	5.1	8.5	11.5
91-100	26.7	35.2	22.2
101-110	35.8	31.6	34.5
111-120	24.8	20.1	23.0
121-130	7.2	3.9	7.2
>130	0.4	0.5	1.9
Mean ± SD *(mm Hg)*	110.2±10.5	107.6±11.3	109.8±12.9
Range *(mm Hg)*	90.0-170.0	80.0-170.0	80.0-180.0

*Effect of trimester (analysis of variance): $p < 0.01$

Table IV
Frequency distribution of diastolic blood pressure (DBP) per trimester of pregnancy* in four rural Guatemalan villages

Categories of DBP (mm Hg)	Trimester of pregnancy First (n=274)	Second (n=364)	Third (n=392)
40-50	1.1	7.4	1.3
51-60	32.1	33.5	27.0
61-70	46.4	41.8	44.9
71-80	16.8	16.5	23.0
81-90	3.4	0.5	3.5
91 100	0.0	0.3	0.3
101-110	0.4	0.0	0.0
>110	0.0	0.0	0.3
Mean±SD	69.0±8.4	66.8±9.0	70.2±8.7
Range (mm Hg)	50.0-110.0	40.0-94.0	50.0-120.0

* Effect of trimester (analysis of variance): $P < 0.005$.

Table V
Frequency distribution of presence of edema per trimester of pregnancy* in four rural Guatemalan villages

Categories of edema	Code	Trimester of pregnancy First (n=242)	Second (n=323)	Third (n=353)
Absence	0	97.5	92.3	89.5
Feet	1	0.8	3.4	3.4
Feet and legs	2	1.7	4.3	6.8
Generalized**	3	0.0	0.0	0.3

* Effect of trimester (analysis of variance): $P < 0.005$.
** Not included in following analyses.

Table VI
Frequency distribution of presence of porteinuria per trimester of pregnancy* in four rural Guatemalan villages

Categories	Trimester of pregnancy First (n=121)	Second (n=167)	Third (n=199)
Absence	81.8	72.5	78.9
Presence	18.2	27.5	21.1

* Effect of trimester (analysis of variance): $P > 0.05$.

depending on the number of surveys performed during pregnancy. Given the scarcity of published data on SBP, DBP, and proteinuria and the heterogeneous methodology used to measure them, it is very difficult to infer conclusions from comparisons with other populations. However, at least in regards to presence of LLE during the third trimester of pregnancy, it is clear that the values in the study population are quite low; the proportion of LLE among women in the four villages was only one fourth of that reported by Thomson (Thomson *et al.*, 1967) for a well-nourished population.

As Table VII indicates, a statistically significant association was observed between supplemented calories during pregnancy (SCDP) and DBP, the dose-response relationship being –0.4 mm Hg per 10,000 supplemented calories during pregnancy. Multiple regresssion analyses were employed to determine the extent to which this relationship changed by controlling the influence of maternal variables listed in Table I. When these maternal factors were entered as independent variables in a multiple regression predicting DBP, the dose-response relationship between caloric supplementation and DBP was basically unchanged, suggesting that the maternal characteristics measured in this study, either alone or combined, could not explain the originally observed association. In addition, the correlation between SCDP and change in DBP from the first to the third trimester of pregnancy was –0.176 ($n = 107$; $b = -0.7$ mm Hg/10,000 SCDP; $P < 0.10$). Given the small sample size it was not possible to select "pathological" cut-off points for DBP and SBP. Therefore, it was decided to choose as breaking points those closest to the upper tercile of the population distribution. These values corresponded to 70 and 110 mm Hg for DBP and SBP, respectively. As Table VII indicates, the percentage of cases with DBP higher than 70 mm Hg was lower in the high- than in the low-supplemented group. The limit (20,000 calories), used to define the high-supplemented group was selected because it predicted risk of being delivered of babies with low birth weight (Lechtig *et al.*, 1975d; Lechtig *et al.*, 1975c); it was close to the increment of caloric expenditure produced during pregnancy in well-nourished mothers, and it would be sufficient to produce an increment of 60 to 240 g. in the average birth weight of this population (Lechtig *et al.*, 1975e).

To explore the possibility that some constant maternal factor might be responsible for both the high consumption of supplement and lower DBP, analyses within siblings of the same mother were performed. Table VII shows the proportion of pregnant women who had a decrement of 20 mm Hg or more in DBP for pairs of siblings divided into three groups. The groups were defined by the differences in caloric supplementation of the mother between two successive pregnancies. When caloric supplementation during the latter pregnancy was lower than during the preceding pregnancy, none of the women showed this decrement in DBP in the latter pregnancy as compared with the preceding one. When caloric supplementation during the latter pregnancy was more than 10,000 calories higher than during the preceding pregnancy, the proportion of women with this drecrement in DBP was 13.9 percent. The intermediate group was composed of siblings in which the difference in caloric supplementation between the latter and the preceding pregnancy was between −9,900 and +9,900 calories. In summary, the analyses in Table VII indicate a consistently inverse association between caloric supplementation and changes in DBP in the entire population groups studied within the same pregnancy and between pregnancies of the same mother.

Table VIII describes the relationship between caloric supplementation during pregnancy and systolic blood pressure (SBP). Although the slope value shows a trend to negative association (−0.2 mm Hg/10,000 calories) the correlations were not statistically significant. The analysis with discrete variables and with siblings did not show significant associations; a similar result was observed when analyzing changes in SBP from the first to the third trimester ($r=-0.022$; $b=-0.1$mm Hg/10,000 SCDP; $n=107$; $P \geqslant 0.10$). However, all 7 cases with SBP $\geqslant$ 130 mm Hg fell within the low supplemented group (t-test: $P < 0.05$).

The discrete variable analyses with three levels of supplemented calories presented in Table IX show a trend in the total sample to a higher proportion of pregnant women with LLE in the high-supplemented than in the low-supplemented group. This trend was also observed within pairs of siblings: the proportion of women with increased LLE during the latter pregnancy as compared with the preceding one was three times higher in those who increased than in those who decreased the amount of supplemented calories (SC) during their latter pregnancy. Moreover, a similar trend was observed in sibling analysis within the "fresco" and "atole" groups (sign test, two independent comparisons, $P = 0.02$). On the basis of these analyses it was inferred that an association existed between increased caloric supplementation and higher frequence of LLE in the pregnant women of this population.

Lastly, the analyses presented in Table X, exploring the relationship between SCDP and proteinuria are contradictory and, hence, difficult to interpret. The analyses across three levels of SCDP showed a weak trend to an inverse association. Given the small sample size involved it was not possible to perform sibling analyses to further explore this relationship. Therefore, no clear association was detected between SCDP and proteinuria.

Discussion

The above results may be summarized as follows: SCDP is inversely related to DBP and directly related to the presence of LLE; no clear association was detected between SCDP and either SBP or proteinuria. Given the fact that caloric supplementation produced a biologically significant increment in the total nutrient intake during pregnancy (Lechtig *et al.*, 1975d), the

Table VII
Relationship between supplemented calories during pregnancy (SCDP) and diastolic blood pressure (DBP) at the third trimester of pregnancy

A. Continuous variable analysis (n = 392)	Correlation value (r)	Slope value (mm blood pressure 10,000 cal)		Probability value (P <)
First order correlation	−0.104	−0.4		0.05
Multiple correlation*	−0.124	−0.4		0.05
B. Discrete variable analysis		Level of SCDP		High minus low (t−test) P <
	Low	Middle	High	
1. Percentage with DBP 70mm Hg > (n = 392)	30.3	19.6	19.7	0.05
	Lower	Similar	Higher	
2. Siblings subsample Percentage with decrement of 20mm Hg or greater in latter pregnancy as compared with preceding pregnancy (n = 135 pairs)	0.0	10.3	13.9	0.01

* Values obtained after controlling for height, head circumference, age, parity, socio-economic status, weight at the end of the first trimester, gestational age, morbidity indicator and home diet within the population with highest coverage (from July 1970 through February 1973).

Slope for total study population greater than slope for population with high coverage (test of covariance: NS). Slope for "fresco" greater than slope for "atole" (test of covariance: NS).

most suitable interpretation of these results is that caloric supplementation during pregnancy caused a decrease of DBP and an increase in the presence of LLE in this population.

Several mechanisms may be proposed to explain the effects herein reported. There is increasing evidence that most of the effect of improved maternal nutrition may be explained by increased hormone secretion, particularly estrogens. Both maternal nutrition and birth weight are directly associated with estriol urinary excretion (Iyengar, 1975); and it is known that increased estrogen production may lead to:

(1) Vasodilatation and consequent decreased peripheral resistance which in turn may lead to decreased blood pressure, particularly of its diastolic component (Hytten and Leitch, 1971).

(2) Changes in the nature and reactions of the ground substance of connective tissue and, as a result, increased hygroscopic capacity of the muco-polysaccharide, with consequent water and salt

Table VIII
Relationship between supplemented calories during preganancy (SCDP) and systolic blood pressure (SBP) at the third trimester of pregnancy

A. Continuous variable analysis (n = 392)	Correlation value (r)	Slope value (mm blood pressure 10,000 cal)	Probability value (P <)
First order correlation	0.003	0.0	NS
Multiple correlation*	−0.044	−0.2	NS

B. Discrete variable analysis	Level of SCDP			Probability value
	Low	Middle	High	(t–test; high minus low)
1. Percentage with SBP 110mm Hg ⩾ (n = 392)	35.9	37.0	34.8	NS
2. Sibling analysis. Percentage with decrement of 20mm Hg or greater in latter pregnancy (n = 135 pairs)	Lower 5.3	Similar 7.7	Higher 12.7	NS

* Values obtained after controlling for height, head circumference, age, parity, socio-economic status, weight at the end of the first trimester, gestational age, morbidity indicator and home diet within the population with highest coverage (from July 1970 through February 1973).

Slope for total study population greater than slope for population with high coverage (test of covariance: NS). Slope for "fresco" greater than slope for "atole" (test of covariance: NS).

Table IX
Relationship between supplemented calories during pregnancy (SCDP) and presence of lower limb edema (LLE) at the third trimester of pregnancy

Discrete variable analysis	Level of SCDP			High minus low
	Low	Middle	High	(t–test) P <
1. Percentage with LLE (n = 353)	7.2	15.4	13.1	0.10
	SC during latter pregnancy were:			High minus low
2. Sibling analysis. Percentage not having LLE in preceding pregnancy and having LLE in latter pregnancy (n = 106 pairs)	Lower 7.7	Similar 14.7	Higher 22.0	(t–test) NS

Table X
Relationship between supplemented calories during pregnancy (SCDP) and proteinuria at the third trimester of pregnancy

Discrete variable analysis	Level of SCDP			High minus low
	Low	Middle	High	(t–test) P <
Percentage with proteinuria (n = 199)	28.6	17.1	22.1	NS

retention in the connective tissue (Hytten and Leitch, 1971; Gersh and Catchpole, 1960; Langard and Hvidberg, 1969), clinically detectable in the lower limbs of pregnant women. Thus LLE would have physiological rather than pathological significance in pregnancy. In turn, the increment of extracellular fluid may decrease the activity of the renin-angiotensin-aldosterone system and, by this means, lead to decreased blood pressure (Hytten and Leitch, 1971).

(3) Increased activity of plasma amino peptidases which may increase the rate of destruction of polipeptides with vasopressor activity in the plasma and, therefore, produce a decrease of arterial blood pressure (Hytten and Leitch, 1971).

These three mechanisms are not mutually exclusive and not necessarily the only ones which may be operating. Given the present state of knowledge, however, they probably represent the most useful models to orient further research in this area.

It is evident that the results presented herein have important implications for nutrition and public health policies, provided that they are replicated by further studies performed on different populations.

On the one hand, the observation that lower limbs edema is produced by improved nutrition during pregnancy is an indication that LLE is a normal phenomenon observed in pregnant women with good nutritional and health status (Hytten and Leitch, 1971) and that its prevalence may be a simple indicator of nutritional status during pregnancy. In our study population, the proportion of women presenting LLE during the third trimester of pregnancy was 10.2 percent, a very low figure when compared to 40 percent in well-nourished normotensive pregnant women of Aberdeen (Thomson, Hytten and Billewicz, 1967). In addition, the presence of LLE may be a gross indicator of adequate fetal growth, useful to predict prognosis during postnatal life.

On the other hand, if improved nutrition during pregnancy lowers DBP, maternal PCM may be one important determinant of the reported high incidence of toxemia in populations of low socio-economic status (Davis, 1971; Neutra, 1973). This may be another pathway through which maternal PCM affects fetal prognosis, since both fetus and placenta of women with toxemia of pregnancy show important alterations in growth and development when compared with the products of conception from normal women (Alvarez *et al.*, 1972; Hendricks and Brenner, 1971; Fox, 1970; Tominaga and Page, 1966; Friedman, Little and Sachtleben, 1962). Thus, to decrease the incidence of toxemia and the associated maternal and infant morbidity and mortality, it may be necessary to ensure adequate nutritional status particularly in those segments of the population at high risk of suffering toxemia when pregnant. In order to increase the efficiency and effectiveness of programs aimed towards the achievement of this goal, simple risk instruments, feasible for use in poor populations with inadequate health services, must be developed (Lechtig *et al.*, 1976a).

Summary

The effects of food supplementation during pregnancy on arterial blood pressure and on the presence of lower limbs edema and proteinuria were studied in four rural villages of Guatemala, in which two types of food supplements were distributed: protein-caloric and caloric. In the combined sample, at the end of the third trimester of pregnancy, the proportion of mothers who had diastolic blood pressure $\geqslant$ 70 mm Hg was 19.7 percent in the high-supplemented group ($\geqslant$ 20,000 cal; n = 173) compared with 30.3 percent in the low-supplemented group ($\leqslant$ 10,000 cal; n = 208; t-test: $P < 0.05$). Although no significant difference was observed at lower cut-off points, all the 7 cases with systolic blood pressure $\geqslant$ 130 mm Hg fell within the low-supplemented group (n = 174) and none was found in the high-supplemented group (n = 180; t-test: $P < 0.05$). In addition, the proportion of mothers with lower limbs edema was 13.1 percent in the high supplementation group (n = 145) compared with 7.2 percent in the low supplementation group (n = 181; t-test: $p < 0.10$). No association was found between caloric supplementation and presence of proteinuria. In the associations reported with diastolic blood pressure and lower limbs edema no significant differences were observed between the protein-calorie and the calorie supplements. These relationships were basically unchanged after controlling for the maternal home diet, height, head circumference, parity, gestational age, duration of disease during pregnancy, and socio-economic status. Moreover, similar associations were found analyzing changes during the same pregnancy and changes in consecutive pregnancies of the same mother. It is concluded that in the rural villages studied, food supplementation during pregnancy produced a decrease in diastolic blood pressure, and increase in frequency of lower limbs edema and no detectable effect on systolic blood pressure nor on proteinuria. The causal nature and possible mechanisms of these findings as well as their public health implications for policies oriented to preventing toxemia of pregnancy are discussed.

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