Indian J Physiol Pharmacol 1993; 37(4): 276-284

A STUDY OF THE EFFECT OF ORAL ZINC SUPPLEMENTATION DURING PREGNANCY ON PREGNANCY OUTCOME

HEMANT K. GARG, K. C. SINGHAL*, Z. ARSHAD**

*Departments of Pharmacology and **Gynaecology & Obstetrics*
J. N. Medical College,
A.M.U., Aligarh - 202 002

(Received on June 28, 1992)

Abstract: Women in different trimesters of pregnancy (Group B; n=106) were administered 200 mg zinc sulphate (elemental Zn 45 mg) orally/day from the day of reporting till delivery. Untreated group of 62 served as control. Levels of zinc in maternal serum, umbilical cord blood serum, and urine were estimated. Pregnancy outcome was assessed in terms of incidence of prematurity, IUGR, birth weight; apgar score and gestational age. Serum zinc levels in Gp. A declined significantly from 113.00±2.80 ug/dl in I trimester to 83.78±2.20 ug/dl in III (P<0.001). Following zinc supplementation (Gp. B) serum zinc levels increased significantly from 109.70+3.23 µg/dl to 205.40±4.47 µg/dl (P<0.001). Urinary excretion of zinc in Gp. A declined significantly with increase in the period of gestation. However in Gp. B, elimination of Zn increased significantly in proportion with the serum levels (P<0.001) cord blood serum zinc level was normal irrespective of maternal serum Zn levels. Following oral Zn supplementation, levels increased significantly from below 127.0 µg/dl to above 158.0 µg/dl in Gp. B (P<0.001). Maternal serum and cord blood serum zinc ratios were fairly constant in Gp. A as well as in Gp. B. Birth weight of babies born with Zn supplementation was significantly higher than control and was related to duration of oral zinc supplementation (P<0.001). Gestational age of babies in Gp. B was significantly higher than respective controls when Zn supplementation was given for more than 3 months (P<0.01), and was related to duration of zinc therapy (P<0.05). As compared to 7 preterm babies in Gp. A, only 2 babies were born preterm in Gp. B (P<0.05). Number of IUGR (SGA) Babies was 9 in Gp A and only 1 in Gp. B (P<0.05) Baby apgar score in Gp. B was significantly higher than respective controls and related to duration of Zn supplementation (P<0.001).

Thus, higher zinc levels in maternal serum, urine, and cord blood serum were associated with better pregnancy outcome. Oral zinc supplementation to pregnant women seems to improve pregnancy outcome, provided it is started early during pregnancy.

Key words : oral zinc maternal serum zinc cord blood serum zinc gestational age apgar score

INTRODUCTION

Zinc is a trace metal, which has been shown to be essential for the growth and well being of rats (1), guinea pigs, chickens, hens and their embryos (2). During pregnancy, there is a physiological decline in plasma zinc; maximum decline being in III trimester (3). Reasons for this decline are plasma volume expansion and consequent hypoalbuminemia; decreased zinc-albumin affinity (4), and increased

*Corresponding Author

fetal demand resulting in mother to fetus transfer of zinc (5).

Zinc deficiency has been reported to cause intrauterine growth retardation (6), premature delivery (7), low birth weight babies (8), and low apgar score (9) in neonates.

The present study was planned to correlate serum, urinary and umbilical cord blood serum zinc levels and pregnancy outcome, and also to study the effect of oral zinc supplementation to pregnant women on pregnancy outcome.

METHODS

Pregnant women reporting to Gynaecology & Obstetrics outpatient and antenatal clinic of J.N. Medical College, A.M.U., Aligarh between Feb. 1991 and April 1992 were included in the study. Pregnancy was established on the basis of history, obstetrical checkup and presence of human chorionic gonadotrophin in urine. Expected date of delivery was calculated from last menstrual period (LMP). Period of gestation was determined and women were placed in three different subgroups according to duration of pregnancy, viz. in I, II and III trimesters.

Exclusion criteria: Exclusion criteria were systemic disease, bad obstetric history, high risk pregnancy, and medication likely to affect pregnancy outcome.

Pregnant subjects were randomly assigned to control (A) and zinc treated (B) groups. Gp. B women were administered a single daily dose of 45 mg zinc as a 200 mg zinc sulphate tablet (Zinfate, Yash Pharma) from the day of reporting till delivery (control group women were not provided zinc supplementation). Subjects were instructed to take zinc sulphate tablets after lunch to avoid gastric irritation. At least five hours were allowed to lapse between the oral administration of zinc and haematinics or calcium to avoid interference with intestinal ab sorption.

Ninety women were randomly assigned to the control group (Gp.A). The break up is given below:

Time of reporting	*Subject included*	*Drop-outs*	*Gp.A subjects selected for study*
I Trimester	30	8	22
II Trimester	30	1	29
III Trimester	30	19	11
Total	90	28	62

Similarly, 120 pregnant women were randomly assigned to zinc treated group (Gp. B). The breakup is given below:-

Time of reporting	*Subject included*	*Drop-outs*	*Gp.B subjects selected for study*
I Trimester	60	22	38
II Trimester	60	4	56
III Trimester	60	48	12
Total	180	74	106

The total number of subjects finally selected in Gp. A was 62, and that in Gp. B, was 106. Data of women who aborted in Gp. A (n=4) and Gp. B (n=2) was not included in this study.

Collection of samples: Five ml non-fasting venous blood and 24 hours urine samples were collected from all subjects, at least once in each trimester and at term. All aseptic precautions were taken, and the plastic vials and glass bottles for blood and urine sample collection were properly washed and sterilized. First sample in Gp. B was always taken before starting zinc therapy. Blood samples were kept at room temperature till serum separated, which was then transferred to fresh vials. At the time of delivery umbilical cord was clamped and cut; fresh jet of blood was directly collected in plastic vials from which serum was separated in the same manner. The serum and urine samples were stored at 4°C, and level of zinc was estimated within 72 hours, by GBC 902 double beam atomic absorption spectrophotometer.

Apgar score of babies was noted after one minute of birth (10). Birth weight (BW) was recorded. Babies with BW less than 2500 g were considered low birth

weight (LBW) babies. Gestational age (GA) of babies was calculated from the 1st day of LMP. Babies born before 37 completed weeks gestation were considered preterm while those born after 42 weeks as post-term. GA and BW were plotted on Lubchenko's weight for gestational age normogram. BW below 10th percentile denoted intrauterine growth regardation (IUGR) or small for gestational age (SGA) (babies). BW exceeding 90th percentile on Lubchenko's normogram denoted large for gestational age (LGA) babies.

Statistical analysis: Statistical analysis of data was done by student's 't' test and 'z' test for proportion.

RESULTS

Serum zinc levels: Serum zinc levels were within normal range in Gp A during I trimester of pregnancy. The levels declined with advancement of pregnancy, attaining significantly low levels in the III trimester of pregnancy (P<0.001). In Gp.B, pretreatment levels of zinc recorded in the I trimester were within normal limits and were not different from Gp.A levels. Following zinc supplementation serum zinc levels increased well above normal (P<0.001), measured on any date within next trimester, but at least 15 days after the previous recording.

The serum zinc levels failed to increase further after attaining a peak, despite continued zinc supplementation (Table I).

Urinary zinc levels: Mean urinary zinc level in Gp. A during I trimester was 231.57±3.76 ug/24 hrs. It declined significantly during II trimester (P<0.001), and was still lower during III trimester (P<0.01). Pretreatment urinary zinc levels in Gp. A compared well with control subjects. Treatment with oral zinc sulphate significantly increased urinary elimination of zinc (P<0.001, Table II).

TABLE I: Duration of therapy related effect of oral zinc sulphate administration 200 mg/day, from the day of reporting till term on serum zinc levels (ug/dl) in pregnant women (Data are $\bar{x} \pm$ S.E.M.)

Group	*Serum zinc level (µg/dl)*						
	Duration of zinc therapy in months						
	6-9			*3-6*		*Less than 3*	
	(Reported in I Trimester)			*(Reported in II Trimester)*		*(Reported in III Trimester)*	
	Pre-treatment	*Post-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
	I Trimester	*II Trimester*	*III Trimester*	*II Trimester*	*III Trimester*	*III Trimester*	*III Trimester*
Group A Control (n = 58)	113.00± 2.80 (n = 19)	99.15[a]± 2.72 (n = 19)	83.78[a][A]± 2.20 (n = 19)	105.10± 1.57 (n = 28)	89.92[a]± 1.62 (n = 28)	85.90± 3.84 (n = 11)	83.40± 4.10 (n = 11)
Group B Zinc treated	109.70± 3.23 (n = 37)	180.16*[A]± 4.85 (n = 37)	205.40*[A][A]± 4.47 (n = 37)	102.72± 1.82 (n = 55)	191.70*[A]± 3.02 (n = 55)	91.25[B]± 3.67 (n = 12)	218.75*[A]± 5.25 (n = 12)

P<0.001
* vs control,
a vs pretreatment,
A vs II trimester post-treatment,
B vs I trimester.

TABLE II : Duration of therapy related effect of oral zinc sulphate 200 mg/day from the day of reporting till term on urinary zinc levels (ug/24 hrs) in pregnant women (Data are $\bar{x}$±S.E.M.).

Group	*Urinary zinc level (µg/24 hrs)*						
	Duration of zinc therapy in months						
	6-9			*3-6*		*Less than 3*	
	(Reported in I Trimester)			*(Reported in II Trimester)*		*(Reported in III Trimester)*	
	Pre-treatment	*Post-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
	I Trimester	*II Trimester*	*III Trimester*	*II Trimester*	*III Trimester*	*III Trimester*	*III Trimester*
Group A Control (n = 58)	231.57± 3.76 (n = 19)	202.78[a]± 3.654.60 (n = 19)	184.21[a,B]± 3.83 (n = 19)	204.46[c]± 3.80 (n = 28)	183.57[d,c]± 6.51 (n = 28)	177.81[c]± 5.99 (n = 11)	170.54[c]± (n = 11)
Group B Zinc treated	242.62*± 1.91 (n = 37)	1211.37**[,a]± 26.22 (n = 37)	1112.46**[,a,A]± 37.76 (n = 37)	247.43**± 3.69 (n = 55)	1187.20**[,a]± 24.77 (n = 55)	277.16**± 16.97 (n = 12)	1019.50**[,a]± 47.40 (n = 12)

P<0.001 ** vs control
a vs pretreatment
c vs I trimester
P <0.01 * vs control
B vs II trimester post-treatment
P <0.05 vs II trimester post-treatment

Cord blood serum zinc levels: Cord blood serum zinc levels in Gp. A in II & III trimesters were 122.69 ±3.31 µg/dl, 116.83±2.19 and 118.54±2.93 µg/dl and were significantly higher than respective maternal serum zinc levels (P<0.001). The levels in Gp. B were 178.64±4.37 µg/dl, 170.58±2.98 µg/dl and 166.45±7.30 µg/dl and did not vary significantly among subjects treated for different durations with oral zinc. However, the levels in Gp. B were significantly higher than respective controls (P<0.001), irrespective of the duration of zinc therapy. The cord blood serum zinc levels in Gp. A as well as Gp. B were significantly higher than respective maternal serum zinc levels at term (P<0.001). Cord blood serum zinc levels in Gp. B failed to increase further after attaining a peak irrespective of the duration of zinc supplementation (Table III).

TABLE III : Duration of therapy related effect of oral zinc sulphate administration (200 mg/day) from the day of reporting till term to pregnant women reporting in different trimesters of pregnancy, on the level of cord blood serum zinc (µg/dl) (Data are $\bar{x}$± S.E.M.).

Group	*Cord blood serum zinc level (µl/dl)*		
	Duration of treatment in months		
	6-9 (Reported in 1 Trimester)	*3-6 (Reported in II Trimester)*	*Less than 3 (Reported in III Trimester)*
Group A Control (n = 58)	122.69±3.31 (n = 19)	116.83±2.19 (n = 28)	118.54±2.93 (n = 11)
Group B Zinc treated (n = 104)	178.64±4.37* (n = 37)	170.58±2.98* (n = 55)	166.45±7.30* (n = 12)

*P<0.001 vs control

Maternal serum and cord blood serum zinc ratios: Maternal and cord blood serm zinc ratio in Gp. A was 1:1.3.

Maternal and cord blood serum zinc ratios in Gp. B were 1:1; 1:1.1 and 1:3, when zinc supplementation was given for 6-9 months, 3-6 months, and 1-3 months respectively. Thus, a more or less constant ratio was maintained between maternal and cord blood serum zinc levels throughout pregnancy in Gp. A as well as in Gp. B subjects. Zinc supplementation did not alter this ratio significantly.

Baby Birth Weight (BW): BW in Gp. A was 2.62±0.05 kg, 2.68±0.04 kg and 2.65±0.07 kg, BW in Gp. B was 3.45±0.04 kg, 3.26 ±0.03 kg and 2.98±0.07 kg, and was significantly higher than respective controls. Moreover, BW of babies born to mothers treated for 6-9 months with zinc was significantly higher than those born to mothers treated only for 1-3 months ($P<0.001$, Table IV).

Gestational Age (GA): The GA of babies in Gp. A was 38.47±0.33 week, 38.30±0.28 week and 38.26±0.43 week. The GA in Gp. B was 39.42±0.13 week, 38.95±0.10 week and 38.83±0.22 week and was significantly higher than respective controls when zinc therapy was given for more than 3 months ($P<0.01$). Moreover, GA in Gp. B subjects treated with zinc for 6-9 months was significantly higher than in subjects treated only for 1-3 months ($P<0.05$, Table V).

TABLE IV : Duration of therapy related effect of oral zinc sulphate administration (200 mg/day) to pregnant women from the day of reporting till term on baby birth weight (kg). (Data are $\bar{x}$±S.E.M.)

	Baby birth weight (kg)		
	Duration of treatment in months		
Group	*6-9 (Reported in I Trimester)*	*3-6 (Reported in II Trimester)*	*Less than 3 (Reported in III Trimester)*
Group A Control (n = 58)	2.62±0.05 (n = 19)	2.68±0.04 (n = 28)	2.65±0.07 (n = 11)
Group B Zinc treated (n = 104)	3.45±0.04* (n = 37)	3.26±0.03* (n = 55)	2.98±0.07*,a (n = 12)

$P<0.001$ * vs control
a vs I trimester

TABLE V : Duration of therapy related effect of oral zinc sulphate administration (200 mg/day) to pregnant women from the day of reporting till term on gestational age of the baby (weeks) (Data are $\bar{x}$±S.E.M.).

	Gestational age of baby (weeks)		
	Duration of treatment in months		
Group	*6-9 (Reported in 1 Trimester)*	*3-6 (Reported in II Trimester)*	*Less than 3 (Reported in III Trimester)*
Group A Control (n = 58)	38.47±0.33 (n = 19)	38.30±0.28 (n = 28)	38.26±0.43 (n = 11)
Group B Zinc treated (n = 104)	39.42±0.13** (n = 37)	38.95±0.10* (n = 55)	38.83±0.22*,a (n = 12)

$P<0.05$ ** vs control
$P<0.05$ * vs control
a vs I trimester

Preterm/post-term babies: In Gp. A, 7 babies were bron preterm while in Gp. B 2 babies were born preterm. There was no post-term baby in either group. The difference in the incidence of preterm babies between Gp. A and Gp. B was significant (P<0.05, Fig. 1&2, Table VI).

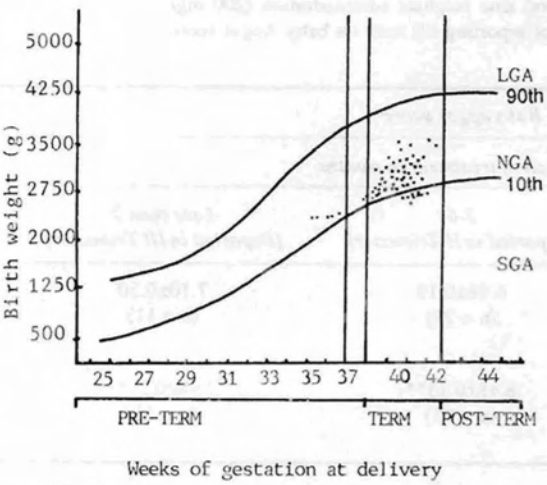

Fig. 1 : Lub-Chenko's weight for gestational age normogram (Gp. A Control)

Lubchenko's weight for gestational age normogram for control subject (n=58)

90th : 90th percentile
10th : 10th percentile
SGA : Small for gestational age (I.U.G.R.)
NGA : Normal for gestational age
LGA : Large for gestational age.

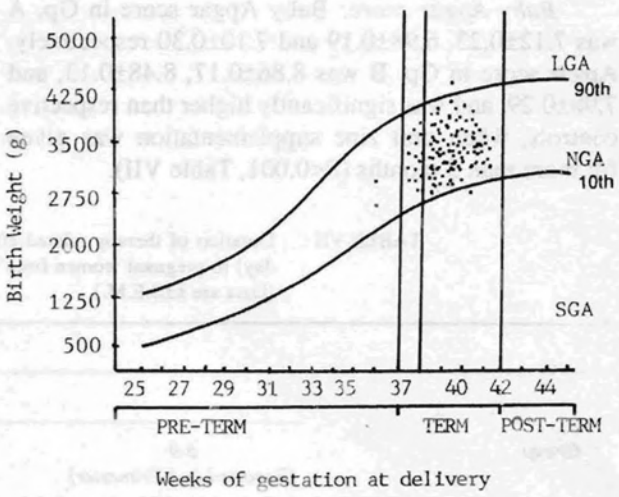

Fig. 2 : Lub-Chenko's weight for gestational age normogram (Gp.B Zinc treated)

Lubchenko's weight for gestational age normogram for zinc supplemented subjects (n=104)

90th : 90th percentile
10th : 10th percentile
SGA : P Small for gestational age (I.U.G.R.)
NGA : P Normal for gestational age
LGA : P Large for gestational age

IUGR (SGA)/LGA babies: IN Gp. A, 9 babies were IUGR/SGA and there was no LGA baby. In Gp. B, there was 1 IUGR baby; there was no LGA baby. The difference in the incidence of IUGR between Gps A and B was statistically significant (P<0.05, Fig. 1&2, Table VI).

TABLE VI : Incidence of birth weight and gestational age related parameters in neonates.

Group	*Number of babies*			
	Preterm babies	*Post-term babies (IUGR) babies*	*Small for gestational age babies*	*Large for gestational age babies*
Control (Gp.A) (n = 8)	7	–	9	–
Zinc treated (Gp. B) (n = 104)	2*	–	1*	1

*P<0.05 vs control

Baby Apgar score: Baby Apgar score in Gp. A was 7.12±0.23, 6.98±0.19 and 7.10±0.30 respectively. Apgar score in Gp. B was 8.86±0.17, 8.48±0.13, and 7.98±0.29, and was significantly higher than respective controls, when oral zinc supplementation was given for more than 3 months (P<0.001, Table VII).

TABLE VII : Duration of therapy related effect of oral zinc sulphate administration (200 mg/day) to pregnant women from the day of reporting till term on baby Apgar score (Data are $\bar{x}$±S.E.M.)

	Baby apgar score		
	Duration of treatment in months		
Group	*6-9 (Reported in I Trimester)*	*3-6 (Reported in II Trimester)*	*Less than 3 (Reported in III Trimester)*
Group A Control (n = 58)	7.12±0.23 (n = 19)	6.98±0.19 (n = 28)	7.10±0.30 (n = 11)
Group B Zinc treated (n = 104)	8.68±0.17** (n = 37)	8.48±0.13** (n = 55)	7.98±0.29*,a (n = 12)

**P<0.001 vs control
*P<0.02 vs I trimeter
aP<0.05 vs control

DISCUSSION

Plasma zinc levels are not only reduced during pregnancy, but the fetal demand for zinc also increases (11). In pregnancy cell proliferation is rapid, extensive, and stretched over a period of nine months. The pregnant mother has to transfer large amounts of zinc to the fetus (6). Animal studies have shown the importance of adequate maternal nutrition for normal fetal growth and development (12). Zinc present in the bones and liver in pregnant rats is not mobilised even under conditions of severe zinc deficiency (13). The maternal nutritional status may not influence serum zinc levels during pregnancy (14). Zinc concentration in maternal tissues influences the neonatal birth weight (7), as zinc in an important coenzyme for high proteosynthetic activity (15). In pregnancy, abnormally low plasma zinc levels are associated with increased maternal morbidity as well as increased risks to the fetus and the new born baby (11). Zinc deficiency may lead to abortions and premature delivery in guinea pigs (16), and humans too (17). Zinc deficiency was found to be responsible for IUGR (6). IUGR is also caused by altered zinc utilization or poor maternal-fetal zinc transfer (18). Zinc deficiency has been reported to cause low apgar score in neonates (9).

Of the total zinc content of human body, only 2.1% zinc is present in blood (19). Estimation of serum zinc, therefore, may not be a true index of zinc deficiency (20). Decline in serum zinc with advancement of pregnancy in this study correlates well with the findings of many other workers (3-5). Serum zinc levels were within normal range during I trimester but declined to below normal levels at term. This is attributed to increase in plasma volume, consequent hypoalbuminemia, decreased zinc-albumin affinity, and addition demand of zinc by foetus (4, 5). The cord blood serum zinc levels were significantly higher than maternal serum zinc levels at term. This signifies transfer of zinc from mother to fetus, and is an expression of the high proteosynthetic activity in fetus, especially in III trimester (3). This also indicates that the fetus receives the required amount of zinc even at the expanse of the zinc pool of its mother.

Serum zinc levels of Gp. B pregnant women increased well above normal after zinc supplementation, but did not increase beyond a certain peak level, even after continued zinc supplementation. This indicates

several events after zinc reaches the maternal blood circulation. This zinc is first supplied through placenta to the fetus (cord blood serum zinc levels were significantly higher even in the face of low maternal serum levels at term). When the fetal zinc demand is met, the maternal body stores of zinc are replenished within 15 days (serum zinc levels of zinc deficient subjects became normal in subsequent serum samples collected after atleast 15 days). Saturation of body zinc stores of mother as well as fetus was reflected by increase in serum zinc levels beyond normal range, and increased urinary excretion of zinc.

Cord blood serum zinc levels did not increase beyond a certain level, which indicates that the fetus does not accept more zinc than is required by it. The maternal serum zinc levels also did not increase beyond a certain peak level despite continued zinc administration. This may mean a decrease in intestinal absorption of zinc and increased urinary excretion of zinc in pregnant women.

In control as well as zinc supplemented women, the ratio between serum zinc and cord blood serum zinc remained fairly constant (1:1.3 in Gp. A; and after 1-3 months zinc supplementations in Gp. B; 1:1.1 in Gp. B after 3-9 months zinc supplementation). This indicates that the levels of zinc in maternal serum and cord blood serum are proportionately correlated. The urinary zinc levels declined with advancement of pregnancy. This signifies the attempt of body at conserving the declining body zinc stores during pregnancy (21). Increased urinary zinc excretion following zinc supplementation obviously points towards elimination of surplus zinc, after saturation of maternal and fetal zinc stores.

The birth weight of babies in zinc treated pregnant women was higher than untreated controls, and was related to the duration of zinc therapy. Highest BW was achieved with 6-9 months zinc supplementation to pregnant women. This shows that zinc deficiency may lead to low BW and oral zinc supplementation improves BW if started early in pregnancy.

The baby apgar score in untreated controls was significantly lower than zinc supplemented subjects. This indicates that zinc deficiency may cause low apgar score in babies and zinc supplementation can improve it. The improvement in apgar score is directly related to the duration of zinc supplementation in the present study.

The gestational age of babies in zinc supplemented subjects was significantly higher than untreated controls, when zinc was given orally for more than 3 months, and the improvement in GA was directly related to duration of zinc supplementation. This signifies that zinc deficiency can adversely affect the GA of babies, and zinc supplementation improves GA, if started early in pregnancy. The number of preterm babies in untreated controls was significantly higher than in zinc supplemented subjects. This signifies that zinc deficiency may lead to prematurity and zinc supplementation during pregnancy has a beneficial role in decreasing the incidence of prematurity.

In control subjects the incidence of IUGR was significantly higher than in zinc supplemented women. This shows that zinc deficiency may be responsible for increased incidence of IUGR, and zinc supplementation may be helpful in reducing IUGR cases.

In the light of the observations made and results obtained, it seems logical to conclude that zinc deficiency may be responsible for increased incidence of prematurity, IUGR, low birth weight, and poor apgar score in the fetus/baby. Oral zinc therapy appears to improve all these parameters as well as the gestational age of babies, especially if started during the I trimester of pregnancy.

A dose of 45 mg elemental zinc/day is well tolerated, and is sufficient to alleviate zinc deficiency during pregnancy. However, there is an inverse correlation between serum zinc and serum copper levels (22). Therefore, to prevent the possibility of hypocupremia, the dose of oral zinc should be reduced to 20 mg/day (as recommended by National Research Council, USA, 1979), when serum zinc levels start rising beyond normal limits.

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