

Studies on Zn, Cu, Mg, Ca and Phosphorus in maternal and cord blood

S. Baig, N. U. Hasnain, Q. Ud-din*

Department of Biochemistry, Ziauddin Medical University and PCSIR Laboratories*, Karachi.

Abstract

Objective: To study the levels of trace elements zinc (Zn), copper (Cu), magnesium (Mg), calcium (Ca) and phosphorus (P) at term and to assess their correlation in maternal and cord blood.

Methods: Fifty two women and their cord blood were studied in a tertiary care hospital in Karachi, Pakistan at the time of delivery. Zn, Cu and Mg were analyzed on atomic absorption spectrophotometer and Ca and P calorimetrically in maternal as well as cord blood. The results were compared with non-pregnant age matched controls.

Results: Compared to controls, levels of Zn, Mg, and P were found higher in maternal and cord blood. Copper levels were found slightly lower in cord blood and Ca was significantly lower both in cord and maternal blood. Babies with birth weight less than 3 kg had higher levels of Zn, Cu and Mg than those with more than 3kg, while reverse was true for the P levels. No significant difference was observed in levels of these elements on the basis of sex of the baby, except the cord blood of the male child had higher magnesium levels than female child. Similarly no significant difference was observed between levels of zinc, copper, phosphorus and magnesium in the maternal and cord blood on the basis of parity, while calcium level were significantly higher in primiparous mothers as compared to multiparous.

Conclusion: The results on the whole suggest that Pakistani women have higher levels of Zn, Cu, Mg and P and a marginal Ca deficiency compared to results of studies around the world (JPMA 53:417;2003).

Introduction

The importance of mineral balance during pregnancy is still underestimated, though diligent research demonstrates that trace elements and minerals are critical for the development of fetus. Many minerals are transferred to the fetus for fetal stores in the latter part of the pregnancy, although they may play important developmental role throughout pregnancy.

Certain essential macro- and micro-minerals are, for instance, constituents of, or interact with enzymes. Without proper enzyme functions, health and immunity suffers.

Magnesium is known to be part of many different enzyme systems and is involved in controlling various metabolic functions. Zinc is a necessary part of hormone systems, and a deficiency of this vital trace element can lead to impaired growth, sexual problems, even diabetes.

It has been shown that various trace elements such as Ca, P, Mg, Zn, Cu, iron etc are metabolically interrelated and there is alteration in their concentration during pregnancy.^{1,2} This study was designed to assess the status of trace elements in maternal and cord blood in the local population during pregnancy.

Subjects and Methods

Fifty-two mothers and their new born infants were studied at the Department of Gynecology and Obstetrics JPMC, Karachi Pakistan. All pregnancies were normal and all women belonged to lower socio-economic group. No supplement was given during the course of pregnancy. Twenty four age matched non pregnant women were studied as controls. Age, parity, obstetric history and social status of the mothers were evaluated to assess the maternity pattern and

after delivery birth weight and sex of the newborn were recorded. Blood was drawn from the mothers immediately after delivery and from the cord while the placenta was still not separated. Trace elements were estimated through Hitachi Z-8000 Atomic Absorption Spectrophotometer with flame atomization.³ Statistical analysis was performed with package statistical Ver 4, Stat soft corporation U.S.A. Student t-test was applied to assess the difference between the means. Pearson Product Moment was used to determine correlation between variables.

Results

Table 1 summarizes trace elements concentration in maternal blood, cord blood and in blood of healthy controls (non-pregnant age matched women). No statistically significant difference was found between the mean Zn, Mg and P concentrations of 52 mothers at term and 24 non-pregnant controls. Copper was found significantly raised ($P < 0.0001$) in maternal blood as compared to cord blood and non-pregnant controls. Calcium levels were the same both in maternal and the cord blood but were significantly low ($P < 0.01$) compared to controls. There was no significant difference between mean Mg and P concentration in maternal, or controls' blood, while Mg and P levels in cord blood were slightly higher. Zinc concentration was significantly higher in cord blood ($p < 0.0001$) compared to maternal and controls. Copper levels were found significantly high in maternal blood when compared with cord blood.

In maternal blood (Table 2) significant positive correlation was found between zinc and magnesium ($p < 0.01$) and zinc and copper ($p < 0.006$). In cord blood positive correlation was found only between Zn and Cu ($p < 0.01$).

Discussion

This study comprised of women belonging to low socioeconomic status who were apparently normal medically and obstetrically. None of the babies had any congenital abnormalities. It is particularly noteworthy that maternal trace elements levels in our population have been found to be higher than those reported in Europeans or Americans but are in accordance with results obtained by Manser and Khan³ for our normal population. Unfortunately these results are only for zinc, copper and magnesium (Table 4). Very few international studies and none locally provide information on the factors that effect trace element levels in normal and abnormal pregnancies. At present for local population there is no epidemiological data to suggest the role that trace elements play in the course of normal pregnancies.

Other studies have shown no significant difference in the levels of trace elements when evaluated against parity.^{1,4,5} The present study showed statistically significant correlation between number of gestations and trace element levels in both mothers and cord blood. Kantola et al⁶ in a study in Finland observed variation in Zn and Cu levels in placenta and maternal blood. Osama et al⁷ showed differences in Ca and Zn levels in multiparous and nulliparous Swedish mothers. Higashi et al⁸ while studying pre-term infants reported that serum levels of trace elements were negatively related to gestation. Our study showed a negative correlation between birth weight and Zn in both maternal and cord blood. Similar observation have been made by others.^{6,9} Arumanayagam et al¹⁰ reported a significant correlation between cord Zn, Cu and birth weight. Zn concentration did not increase significantly after the 35th week; Zn supplementation increased the birth lengths¹¹, but had no effect on birthweight.¹² Higher Zn levels observed by Goel and Misra¹³ in female babies has been attributed to higher requirements of Zn by females who have higher growth potential compared to males. Extreme deficiency of Zn results in congenital malformation in fetus.^{5,9,16} Observations by Ward et al¹⁷ on Gujrati women living in India and England or by Osendarp et al¹⁸ on Bangladeshi women showed no requirement for Zn supplementation during pregnancy. Our results on Cu levels in mother's blood are in accordance with the previous findings.¹⁹⁻²¹ The increase in Cu levels could be related to synthesis of ceruloplasmin, a major Cu binding protein.

Plasma or serum Zn concentration falls by 20-25 percent during pregnancy.¹³ But in the present study maternal blood levels were not significantly different from non-pregnant controls. May be there was an initial fall in Zn levels which was later on recovered at the time of delivery; or there may have been no change in Zn levels throughout pregnancy.

Since serum or plasma Zn concentration are depressed by trauma, infections and corticosteroids as well as by estrogens, they are unreliable indicators of Zn status even in non-pregnant individuals. In another study¹⁴ a positive correlation between plasma Zn at delivery and infant birth weight was found. In the present study although the maternal Zn levels were same in pregnant and controls but correlation of Zn with birth weight was found negative.

A positive correlation was observed between Zn and Cu in maternal and cord blood and Zn and Mg in maternal blood but none between birth weight and maternal and cord blood Zinc content. Zinc concentration in maternal and cord blood did not differ between male and female new borns.⁵ Some reports¹⁵ indicate that maternal iron supplementation or therapy may have an adverse effect on Zn status. In cases where Zn intake is already low or inadequate, supplementation of iron might possibly reduce its availability to the fetus to an extent that it could compromise fetal growth. A large number of congenital malformations in fetus could be related to low maternal levels of Zn as has been shown in various experimental studies in human beings.^{9,16} But they are probably only to be seen in instances of extreme Zn deficiency.⁵ Such event seems unlikely to occur here and therefore there appears to be no requirement for general Zn supplementation during pregnancy. Observations made by Ward et al¹⁷ were somewhat similar while studying Gujrati women living in India and England. They found no difference in plasma concentration of Zn at 28 weeks between any of the dietary groups whether vegetarian or non-vegetarian, living in India or England. Supplementation of diet with elemental Zn during the last two trimester of pregnancy did not improve birth outcome in Bangladeshi study.¹⁸

Furthermore, the biological significance of low Zn levels in cord blood found in the present study could be subjected to further investigations. Infants in this group were normal with normal birthweight. Low values in cord blood are in comparison to maternal values, maybe they are not low in comparison to international standards.

The increase in Cu in the blood also depends on the time of gestation. It has been observed that maternal serum Cu levels are elevated from the luteal phase of the pregnancy and rise with the progression of pregnancy.¹⁹ In comparison to non-pregnant women, normal pregnancies near term had higher levels of Cu.²⁰ Although at term total serum concentration of Cu in the mothers was approximately twice that of normal non-pregnant value, the percentage of free Cu was not significantly changed.²¹ It is caused by a parallel increase in Cu's major binding protein ceruloplasmin increased as a result of elevated levels of maternal estrogen. Copper concentration increase during the last 3 months of pregnancy and decrease after delivery. The decline is slower in women who breast-feed.²² In cord blood Cu levels were found to be significantly higher in infants below 3 kg of weight ($p < 0.05$) than infants born above 3 kg of weight. Small for gestational age infants (SGA) had higher serum Cu concentration than reference infants. Babies with birth weights of less than 1000g had higher serum Cu concentration at one week than those with birth weights of 1000 to 1500g. Serum Cu concentration in malformed infants did not differ from the concentration in reference infants. When mean Cu levels were checked in vegetarians and non-vegetarians, living in India and England, the plasma Cu levels showed the same trend in all the four groups.¹⁷ Mothers who gave birth by vacuum, forceps or caesarian section tended to have lower serum Cu values than reference mothers.²²

Hypomagnesemia during pregnancy has been attributed to hemodilution and to estrogen domination to which these women are exposed.²³ Mg levels significantly decreased during 9th month of ges-

levels were reported to be higher in Pakistani women compared to levels elsewhere in the world. This higher level may be related to the higher consumption of dal (cracked legumes cooked to a soup-like consistency) and possibly to higher Mg levels in the water supply. The water supply in Karachi has not been analyzed but the glacial sources in Pakistan has been reported to contain 1.260 mg/L of Mg.²⁶ There are many studies on the physiologic functions, pathologic disturbances and therapeutic applications of Mg. Current evidence in a study in UK suggests pregnancy associated growth is unlikely to cause maternal Mg deficiency and that there is no such requirement for Mg supplementation during pregnancy.²⁷

Of all the rigid structure building elements, Calcium is the one where deficiency is a possibility and this is particularly true for expectant and lactating mothers who have to provide extra Ca for the development of bones in the fetus, or provide milk for the newly born infant. Maternal Ca levels in the present study were also found slightly but significantly lower than controls ($P < 0.01$). The decline begins shortly after conception and is progressive until the middle of the third trimester after which there is a slight rise. One gram of albumin binds 0.7 mg of Ca. An average fall in serum albumin of 0.9 gm per 100 ml and during normal pregnancy should result in a fall of 0.1 mg of calcium per 100 ml.²⁸ Conservation of Ca can be seen by decreased urinary excretion during pregnancy that is at the time of maximal fetal requirement. This has been observed in patients who continue their usual diet. On the other hand high excretion persisted throughout pregnancy in patients whose diet was supplemented with vitamins and minerals. This proves that the supplement was superfluous and in excess to their endogenous requirements and it obscured the organism's intrinsic mechanism of adaptation. In the present study cord serum Ca levels were slightly but not significantly higher than maternal levels.

Serum inorganic phosphorus (P) exhibits a slightly different pattern, falling progressively until approximately 30 weeks, at which time a drop of 6 percent from non-pregnant levels can occur and then rising to nearly non-pregnant levels by term.²⁸ Levels of P checked at the time of delivery were found similar to non-pregnant levels in the present study. This also confirms another report²⁴ that inorganic phosphorus levels decreased significantly during the 9th month of gestation ($P < 0.01$) but rise to non-pregnant levels in labour.

Fetal content of both Ca and P is related to fetal weight in a linear manner. It has been reported that serum Ca levels in the fetus exceed those in the mother by some 1 to 2 mg per 100 ml. This relationship has been recognized for more than 50 years and has been confirmed repeatedly.²⁸ Quite clearly, regulation of fetal Ca and P metabolism is a complex process. Available data regarding endocrine activity depressed PTH and elevated CT levels indicate a situation favorable for skeletal growth. These hormonal changes in the adult would result in a lowering of serum Ca and yet the fetus is hyper-calcemic with respect to mother. Therefore, it appears that other factors, such as the placenta, must play a major role in regulating the serum Ca levels in the fetus.²⁸

Conclusion

The results on the whole suggest that Pakistani women have more pronounced levels of Zinc, Copper, Magnesium and Phosphorous and a marginal Calcium deficiency compared to studies around the world. In pregnancies with complications further studies regarding trace elements levels in blood in local population are required.

References

1. Tsang RC, Zlotkin SH, Nichols BL, eds. Nutrition during infancy: principles and practice. 2nd edition. Cincinnati Digit Educat Pub 1997.
2. Olatunbosun DA, Adeniyi FA, Adadevok BK. Serum calcium, phosphorus and magnesium levels in pregnant Nigerians. *Br J Obstet Gynecol* 1975;82:568-71.
3. Manser WT, Khan A. Trace elements studies on Karachi population: normal ranges for blood copper, zinc and magnesium for adults. *J Pak Med Assoc* 1989;39:43-9.
4. Adeniyi FAA. The implication of hypozincemia in pregnancy. *Acta Obstet Gynecol Scand* 1987;66:579-89.
5. Marsal K, Furgyik, S. Zinc concentration in maternal blood during pregnancy and postpartum, in cord blood and amniotic fluid. *Acta Obstet Gynecol Scand* 1987;66:653-6.
6. Kantola M, Purkunen R, Kroger, et al. Accumulation of calcium, zinc and copper in maternal blood and developmental placental tissue: differences between Finland Estonia and St. Petersburg. *Environ Res* 2000;83:54-66.
7. Osama K, Akesson A, Berglund M, et al. Toxic and essential elements in the placentas of the Swedish women. *Clin Biochem* 2000;33:131-8.
8. Higashi A, Tajiri A, Matsukura M, et al. A prospecting survey of several maternal serum. Zn level and pregnancy outcome. *J Pediatr. Gastro Nutr* 1980; 7:430-3.
9. Hurley L.S. Trace Element in Prenatal and Neonatal Development : zinc and manganese. Trace elements in nutrition of children. New York: Raven Press 1985, pp. 121-32.
10. Arumanayagam M, Wong FWS, Chang AMZ, et al. Zinc concentration in umbilical cord tissue and cord plasma in appropriate for gestational age babies. *Eu J Obstet Gynecol Reprod Biol* 1986;23:121-6.
11. Rivera AJ, Ruel MT, Santizoc, et al. Zinc supplementation improves the growth of stunted rural Guatemalan infants. *J Nutr* 1998;128:556-62.
12. Osendarp SJM, Raaij JMAV, Darmatadt GL, et al. Zinc supplementation during pregnancy and effects on growth and morbidity in low birth weight infants: a randomized placebo controlled trial. *Lancet* 2001;357:1080-5.
13. Goel R, Misra PK. Study of plasma zinc in neonates and their mothers. *Indian Pediatr* 1982;19:611-14.
14. Aggett PJ. Extra zinc in pregnancy. *Contemp Rev Obstet Gynecol* 1989;181-9.
15. Bloxam DL, Williams NR, Waskett RJD, et al. Maternal zinc during oral iron supplementation in pregnancy: a preliminary study. *Clin Sci* 1989;76:59-65.
16. O'Brian KO, Zavaleta N, Caulfield LZ, et al. Prenatal iron supplements impair zinc absorption in pregnant peruvian women. *J Nutr* 2000;130:2251-5.
17. Ward RJ, Abraham R, Mefaydyen IR, et al. Assessment of trace element intake and status in a Gujarati pregnant Asian population and their influence on the outcome of pregnancy. *Br J Obstet Gynecol* 1998;95:676-82.
18. Osendarp SJ, Van-Raaij JM, Arifeen S. A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy outcome in Bangladeshi urban poor. *Am J Clin Nutr* 2000;71:114-9.
19. Nicols BL, Nicols VN. Nutrition in pregnancy and lactation. Nutrition abstracts and reviews in clinical nutrition. 1983;259, 53.
20. Reyes H, Baez ME, Gongalez MC, et al. Selenium, zinc and copper levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. *J Hepatol* 2000;32:542-9.
21. Arnaud J, Prual A, Freziosi, et al. Effect of iron supplementation during pregnancy on trace elements (Cu, Se, Zn) concentrations in serum and breast milk from Nigerian woman. *Ann Nutr Metab* 1993;37:262-71.
22. Bro S, Berendtsen H, Norgaard, et al. Serum zinc and copper concentration in maternal umbilical cord blood: relation to course and outcome of pregnancy. *Scand J Clin Lab Invest* 1988;48:805-11.
23. Dale F, Simpson G. Serum magnesium levels of women taking an oral or long term injectable progestational contraceptive. *Obstet Gynecol* 1992;39:115-19.
24. Sherwani S, Hasnain N, Qadiruddin. Magnesium Status in maternal and cord blood. *J Pak Med Assoc* 1998;48:32-3.
25. Keller WD. Chemical analysis of water used in Hunza, Pakistan. In: Hemphill DD ed. Trace substances in environmental health. XIII Columbia MO University of Missouri 1979;130-7.
26. Husain SM, Sibby CP. Magnesium and pregnancy. *Miner Electrolyte Metab* 1993;19:295-307.
27. Pitkin RM. Calcium metabolism in pregnancy. A review. *Am J Obstet Gynecol*. 1975;1:724-37.
28. Goss DA. Renal conservation of calcium during pregnancy. *Obstet Gynecol* 1960;20:199-203.