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The Effect of New Therapy Zinc on Perinatal Mortality, Prematurity and Placental Ablation

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Sardjana Atmadja [1]
Faculty of Medicine of Syarif Hidayatullah Islamic University[1]
Jl. Ir H. Juanda No. 95, Cemp. White, District. Ciputat Tim., South Tangerang City, Banten[1]
Indonesia[1]
e-mail: sardjana@uinjkt.ac.id[1]

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Abstract

Zinc is essential for life and is a part of zinc finger proteins, which perhaps represent the largest class of DNA-binding proteins. Zinc finger protein controlled gene expression may be a fundamental aspect of development as well as other processes. Nearly 30 elements are accepted as being essential for some or all organisms. Knowledge of the amounts of zinc in food is necessary for the understanding of the very complex system of zinc metabolism. Zinc content in leucocytes, mononuclear cells, red cells and platelets could be used as a measure of possible zinc deficiency. Almost 300 different enzymes, which include the synthesis and/or degradation of all major metabolites, have zinc as an integral component. AE has been interpreted as being a zinc-deficiency disease. The signs and symptoms of AE are reserved by zinc therapy. The recommended daily intake of zinc in pregnancy and lactation is 15 mg in Sweden and the Scandinavian countries. A woman on continuous zinc therapy for AE had two normal pregnancies. Other contributors to this volume will review these data.
Keywords: Zinc

1. Introduction

Zinc is essential for life. It is necessary for growth and is a part of zinc finger proteins, which perhaps represent the largest class of DNA-binding proteins. Zinc finger protein controlled gene expression may be a fundamental aspect of development as well as other processes[1]. The requirements for zinc and the other essential chemical elements of the periodic system are the most basic needs to be met with in pregnancy. Nearly 30 elements are accepted as being essential for some or all organisms[2]. Knowledge of the amounts of zinc in food, its bioavailability, uptake mechanisms, distribution, redistribution, storing, elimination and specific zinc-dependent processes is necessary for the understanding of the very complex system of zinc metabolism.

Measurement of serum, plasma, salivary, seminal, hair or amniotic fluid zinc concentrations; urinary, sweat, and fecal zinc excretion; and estimations of zinc content in leucocytes, mononuclear cells, red cells, of platelets have all been used in clinical work[3]. Almost 300 different enzymes, which include the synthesis and/or degradation of all major metabolites, have zinc as an integral component. Yet it has been possible to agree upon one specific enzyme activity that could be used as a measure of possible zinc deficiency in clinical routine[4].

In human, acrodermatitis enteropathica (AE) has been interpreted as being a zinc-deficiency disease. The signs and symptoms of AE are reserved by zinc therapy. Seven pregnancies have been reported in AE women not on zinc therapy[5]. Two AE mothers gave birth to babies with

malformations, one had an anencephalic fetus, the other an achondroplastic dwarf. Two other babies were of low birth weight. A woman on continuous zinc therapy for AE had two normal pregnancies.

In experimental animal studies, very important and comprehensive work has been done. Studies of zinc deficiency induced in different ways have shown that a normal and adequate zinc balance is necessary for formal fertility, implantation of the egg, normal fetal development, normal pregnancy and parturition, lactation, and further infant growth and development. Other contributors to this volume will review these data[6].

The present officially recommended daily dietary safe adequate intake of zinc in pregnancy and lactation is 15 mg in Sweden and the Scandinavian countries. The calculated mean daily dietary zinc intake in young first-time pregnant women in Sweden was 9.4 mg. available data indicate that the real intake of zinc in other well-development countries with high socioeconomic status is lower the recommended[7].

2. Research Method

Allowance. When the diets are low in protein content, zinc intake is still lower, which has been studied in patients on chronic dialysis, for example. Maternity zinc deficiency can cause **disruption of the physical and intellectual development of the fetus** [8]**. Forpregnant women who consume zinc 15mg per day, the fetus will show the development of liver function and motor yang good,** the fetus will be more active compared with pregnant women who did not take zinc properly[9]. Zinc reacts as a neurotransmitter that plays a role in the maturation of cells as well as in early growth and development of fetal life sar af and their intelligence in the future. In short it functions and Benefits of Zinc:

- improve brain function
- strengthen the fetus for pregnant women
- prevent jaundice in babies born early
- overcome weak memory
- prostate problems for men

2.1 Bioavailability

Bioavailability of zinc from food is variable and is influenced by many factors, such as the dietary contents of calcium; trace elements such as iron, copper and tin; heavy metals such as cadmium, mercury and lead [10]; the amounts and types of fibers, tannins, phytates, oxalates and soy protein; drug treatment such as antacids, ethambutol, hydroxyquinolines, penicillamine, phenytoin, tetracycline, diazepam, disulfiram, acetazolamid, captopril and metronidazol; and the function of the proximal gastrointestinal area and gastric acid production, which in turn is effectively inhibited by histamine receptor blockers, protone pump inhibitors and anticholinergic drugs. Adults on a diet containing 10.7 mg of zinc and rich in fibres and oxalic acid had a negative zinc balance[11], [12]. Zinc absorption was impaired when 16 g of bran was added to a diet giving 12.9 mg of zinc. Relatively small amounts of animal protein could significantly improve the value of a legume-based meal as a source of zinc. The amount of zinc absorbed from the meals was strongly correlated with both the protein and zinc content[13]. The fermentation of bread containing bran reduced the phytic acid content and increased zinc absorption from such bread. Food preparation that decreased the phytic acid content improved zinc absorption. Milk as well as lactose-free milk significantly reduced zinc absorption in a group of women.

2.2 Uptake

Uptake of trace elements is an active, controlled process in the proximal part of the gastrointestinal area. The production of the low-molecular-weight protein metallothionein in the mucosal cells is induced by copper, zinc, and heavy metals such as cadmium and mercury, but also by acute-phase reactions, ACTH, corticosteroids, and interleukin-1 release[14]. Metallothionein-metal complexes could be retained in the mucosal cells and expelled into the lumen. The binding protein may act as a barrier blocking the unnecessary uptake. Manganese

and iron share absorptive pathways different from the absorption of zinc. Manganese inhibited iron absorption but not zinc. An intraluminal interaction may occur between zinc five-fold in excess to iron in water solution, but not with a hamburger meal[15]. Zinc uptake from oral test solutions is reduced in patients with proximal intestinal damage and villous atrophy of varying degree. Patients with folate deficiency had a lower uptake than those who had gotten folate therapy before testing, indicating that folate deficiency in some way accelerates the defects in zinc mucosal uptake. In patients with intestinal bypass operations, Crohn's disease, and in pancreatic insufficiency, zinc uptake from test doses is reduced. When the proximal gastrointestinal surface is damaged, either by gastric resections, autoimmune mucosal gastric atrophy of different degrees, duodenitis, or villous damage of increasing degree (as in celiac disease), there is a stepwise increase in the frequency of zinc deficiency of zinc deficiency. Zinc deficiency in these situations is more frequently met with than folate deficiency. When folate deficiency is present, it is almost always simultaneous with zinc deficiency.

2.3 Distribution

Plasma zinc levels in man follow a circadian variation. The time course of plasma cortisol fluctuations paralleled that that of zinc. Circulating zinc levels in blood decrease in acute-phase reactions as fever increases, which was shown already by Vikbladh in 1951. Later on Falchuk showed that ACTH administration reduced serum zinc and that the response dependent on the initial serum zinc content. Both in the acute disease and during ACTH infusion, the decrements in total serum zinc were the consequences of reductions in the zinc content of the proteins in the fraction consisting of albumin and β-globulins. Later it was found that the acute-phase reaction induces increased production of metallothionein, which subsequently redistributes zinc. A similar redistribution takes place for iron but is effected by specific iron-binding proteins and parallels that of zinc.

Depressed levels of transport proteins are found secondary to zinc deficiency. Such low levels of albumin, transferring, and prealbumin in serum were improved or corrected when zinc therapy was given[16]. Similar effects, including improved levels of retinol binding protein and coagulation factors, were registered in patients with alcoholic liver disease after zinc supplementation.A redistribution of plasma zinc between albumin and α-2-macroglobulin takes place in the second and third trimesters of pregnancy, which might represent an adaptive response designed to reduce eventual adverse effects of lowered plasma zinc concentrations on the developing fetus.Depressed serum zinc levels were found in diabetic patients with secondary organ complications when compared with those without complications. The lowered zinc levels could not be explained by lowered albumin levels and were probably secondary to hyperzincuria. Particularly low zinc levels were found in a group of diabetic males with polyneuropathy and impotence.

In catabolism there is a redistribution of elements. Plasma or serum zinc levels are falsely or secondarily increased. The same redistribution happens in hemolysis and if blood samples are drawn after prolonged stasis.Zinc is stored in the liver. Patients treated with diuretics had lower liver zinc content than untreated ones. Zinc stores in young women seem to be small and were easily depleted when an experimental zinc-deficient food was given. Low hepatic zinc levels indicating zinc deficiency occur not only in alcoholic cirrhosis but also in less advanced alcoholic as well as in nonalcoholic liver disease, as chronic active hepatitis and chronic persistent hepatitis[17].A change in zinc distribution is also found in thyroid disease. In hyperthyroidism serum zinc levels were increased and whole-blood zinc reduced. In hypothyroidism the reverse was observed; serum zinc levels were decreased and whole-blood zinc increased.

2.4 Elimination

Elimination of zinc is mainly enteral. Increased zinc losses are seen in acute and chronic diarrheas. In steatorrhea there are complex losses of different elements and lipid-soluble vitamins. The more lipids lost, the lower are the serum zinc levels[18]. Evidence of zinc deficiency in patient with chronic inflammatory bowel disease has been presented. Long-time treatment with chelating drugs, for example ethambutol, affects zinc nutrition and induces damage to the tapetum lucidum in the eye. To counteract this, zinc therapy has been suggested. Several of the drugs mentioned earlier could also affect uptake and distribution of zinc and other metals and alter their elimination, and thus could have teratogenic potential. The elimination of

zinc is increased in polyuric subjects, for example, in diabetics with bad metabolic control, in alcoholics, and in hypertensive subjects treated with diuretic drugs that result in lowered liver zinc levels.Cutaneous zinc losses increase when sweat losses are increased, as well as in patients with burn and dermatitis[19]. Zinc deficiency could also be manifested as skin changes with hyperkeratosis and dermatitis. The zinc content of normal hair is high compared with other tissue. Serum zinc levels are low in a great number of disease and conditions known to cause alopecia.Zinc balance has been studied in young, nonpregnant women who were given an experimental diet containing 0.17 mg zinc daily. During the study serum zinc levels decreased 21 to 47%, and urinary zinc excretion decreased. Within one month 7 out of 10 subjects developed symptoms of sore throat, diarrhea, taste complaints, and dermatological changes. It was suggested that accessible zinc stores were not extensive and that depletion of these stores caused the fall in serum zinc.

2.5 Zinc in Pregnancy

Zinc balance has been studied in pregnancy. A mean total daily zinc loss of 3.6 mg/day was found. The apparent net zinc absorption was 25% of the mean intake of 29.4 mg zinc/day. In another study the mean prestudy intake was 17 mg zinc/day and during the study 20 mg zinc/day was given[7]. The apparent retention was 2.4 mg zinc/day; dermal losses were not measured. The fasting salivary zinc levels were significantly lower than in controls and increased as the study, which involved higher zinc intake than before, proceeded. Serum zinc levels increased slightly as did urinary zinc excretion. The total zinc requirement during the last half of human pregnancy may be about 2.6 mg absorbed zinc/day[20].We have studied zinc metabolism in human pregnancy prospectively on the theory that serum zinc levels during pregnancy reflect the patients actual zinc status. We wanted to examine whether serum zinc measurement could prove useful in predicting complications affecting mother and/or child and if zinc therapy could be of any benefit[9].

We found that the serum zinc levels decreased gradually during the first and second trimester, as was already shown by Berfenstam in 1952. A selected group of normal women, however, who gave birth to normal infants by normal deliveries at the normal time, showed a very slight and slow fall in serum zinc concentrations during their pregnancies. No recordings were distinctly outside the normal range of serum zinc for non pregnant, healthy, fertile women of the same age and social background[8]. Women delivering before or after normal term had lower serum zinc concentrations during their early pregnancies than women delivering in the 40th week of gestation. Women with abnormal deliveries, especially inefficient labor and atonic bleeding, showed lower mean zinc concentration during early pregnancy than women with normal deliveries. Women who gave birth to immature or dysmature infants showed lower mean serum zinc concentration during early pregnancy than women with normal deliveries and normal infants. In our first studies we registered ten infants with congenital malformations. In six cases maternal serum zinc levels were the lowest we registered compared with levels in mothers with the same length of gestation and normal babies. A few mother who later developed missed abortions showed lower serum zinc levels than those who aborted spontaneously.

2.6 Zinc Therapy

FThe first zinc therapy trial included a group of 20 women with unsatisfactory hemoglobin levels, in spite of treatment with iron and vitamin supplementation, who also had low serum zinc levels. Seven women were assigned at random to zinc therapy, the others to control. Zinc therapy, in a manner similar to the accepted, usual iron therapy, was given in a dose of 90 mg Zn/day as citrate. After one week's therapy, serum zinc levels and urinary zinc excretion increased significantly. Three women on zinc therapy reported improvement in sense of taste[12]. The zinc-treated women had a more favorable outcome of their pregnancies, another duration of labor, and less bleeding. Side effects were not seen.

In a further study were recorded serum zinc values 312 women in the 14th week of gestation. Half of those with initially low serum zinc levels < 10 µmol/1, were randomly assigned to oral zinc therapy, half to control. Zinc sulphate in an effervescent preparation giving citrate corresponding to 45 mg Zn/day was given throughout pregnancy to 64 women during the second and third trimester. The frequency of normal deliveries with normal babies was higher,

63%, in the therapy group than in the control group of 69 women with initially low serum zinc levels (48%) and compared with the women initially high serum zinc levels (55%). The number of prolonged gestations and postmature babies was reduced in the zinc therapy group. Untreated women with initial serum zinc levels below the mean, 10.3 µmol/1, and subsequently decreasing levels, 14th to 36th week, delivered normal infants normally only in 26% of the cases. Side effects of zinc treatment, expect nausea in some cases, were not registered[21]. Serum copper levels in the 36th week of gestation did not differ between the zinc treatment and the low control groups. From these two small randomized studies we learned that oral zinc therapy for women with low serum zinc levels in early pregnancy was tolerated and could reduce some of the risks we earlier had identified.

On the basis of our experiences, an open zinc therapy study was started on the theory that low fasting serum zinc indicated zinc deficiency, which could be treated. The results have been published. All pregnancies during a period of four years (2011 through 2014) in the small country of Soderhamn were included. The area has nearly 32,000 inhabitants and one mother care unit (MCU) at the hospital in Soderhamn. A total of 1345 pregnant women registered at the MCU during these years. One women emigrated, 17 had legal abortions, and 96 had spontaneous abortions. The remaining 1231 mothers gave birth to 1235 children. Additionally, 60 to 70 women per year had legal abortions performed, but were never registered at the MCU. Fasting serum zinc (fS-Zn) analysis was done when gestational problems, anemia, fatigue, or cravings appeared, or if earlier pregnancies had been complicated by miscarriages or abnormal deliveries, as an active measure with the intention of discovering zinc deficiency[22]. In follow-up controls during the second and third trimester, serum zinc samples were drawn more than two hours after breakfast but before noon. Serum zinc was assyed by atomic absorption spectrophotometry. All sampling and handing were carefully standardized in order to avoid stasis, hemolysis, and contamination. In 1984 all mothers (n = 352) had their zinc levels controlled at the first MCU visit (mean ninth week of gestation). Zinc therapy was given if fS-Zn was lower than normal according to the length of gestation (<10.5 µmol/1 in the first or second trimester, < 9.5 µmol/1 in the third)[20]. The normal zinc dose was 22.5 mg Zn as citrate from an effervescent zinc sulphate preparation giving citrate. The dose was increased to 45 mg or in some cases to 90 mg/day if fS-Zn levels did not increase. In 1986 a multivitamin preparation containing zinc citrate corresponding to 15 mg Zn was also used. Iron therapy was given if B-hemoglobin levels decreased 115 g/1. iron preparations were not administered within four hours of the zinc dosage.

Pregnancy controls followed the same standardized Swedish MCU scheme all four years. Delivery records were also kept according to such standard protocols. Diagnostical procedures followed the official statistical WHO classification. Perinatal mortality was defined according to the WHO recommendations of March 30, 2011. Preterm delivery was defined as birth before 37 completed weeks of gestation. The perinatal period commences at 22 weeks of gestation and ends seven completed days after birth. The study was approved by the Swedish Board of Health and Welfare and the Ethics Committee of the University.

The controls 2012 showed a mean fS-Zn of 11.3 µmol/1; SD of 1.6; n = 352. mean B-hemoglobin was 128 g/1; SD was 9. S-albumin and fS-Zn correlated positively, r-0.43. No correlation was found between fS-Zn and B-hemoglobin, S-alkaline phosphatase, or S-urea.

Zinc therapy was given totally to 598 women, noncompliears included. Compliance was controlled by interview and was high. During the first year of the study, the canges in serum zinc between the first and third trimester were calculated. Untreated women showed decreasing levels: mean – 1.4 µmol/1;SD = 2.9; n = 25; $p < 0.05$. Those on 22.5 mg Zn showed: mean 0.72 µmol/1; SD = 2.2; n =32; $p < 0.01$. Those on 45 mg Zn showed: mean 2.18 µmol/1; SD = 1.9; n = 13; $p < 0.005$.

In the zinc-treated group, two children died perinatally (2/598 deliveries). Thirteen children died perinatally among 633 women without any zinc supplementation. The null hypothesis of an even distribution of perinatal fetal deaths could be rejected using Fisher's exact probability test, pp < 0.01.

Preterm delivery occurred in 82 cases. These 82 mothers gave birth to 84 babies. In the zinc therapy group 36 out of 598 (6%) gave birth preterm to 38 babies; one was born in the 30th and another in the 31st week; the others were born later than the 33rd week, 20 of these in the 36th week of gestation. In the unsupplemented group 46 out of 633 (7.3%) give birth to 46 preterm

babies, 14 of which sere born before the 33rd week of gestation, eight of which before the 27th week. Thus 2 out of 598 women treated with zinc and 14 out of 633 untreated women had preterm deliveries before the 33rd week of gestation[23]. The null hypothesis of an even distribution of preterm deliveries irrespective of therapy can be rejected using the chi-square test with Yates's correction, $p < 0.01$.

Placenta ablation, totally of partially, occurred in 8/633 unsupplemented cases but did not occur among 598 women on zinc therapy. The null hypothesiscan be rejected using Fisher's exact probability test, pp = 0.008.

Spontaneous abortions occurred in 96 out 1327 registered pregnancies (7.8%), 17 legal abortions excluded. Among women who had their zinc therapy instituted early in pregnancy before the 22nd week of gestation, 5 out of 177 cases had spontaneous abortions (2.8%); among those untreated before the 22nd week, 99 out of 1150 (7.9%) aborted. The null hypothesis of an even distribution of the abortions irrespective of therapy can be rejected using the chi-square test, $p < 0.05$.

Side effects from zinc therapy were not seen except for nausea in some cases. Serum copper levels in the third trimester were not altered zinc therapy. The frequencies of diabetes and hypertension as well as smoking did not differ between the groups. Normal fS-Zn levels in healthy, fertile women from this part of Sweden were mean 12.3 µmol/1 (SD = 1.0), S-albumin mean 44.2 g/1 (SD = 2.3). women using contraceptive pills had a mean fS-Zn of 11.8 µmol/1 (SD = 1.3), S-albumin mean 40.8 g/1 (SD = 2.2). fasting serum zinc levels in 86 women aged 16 to 44 years from in ongoing series of biopsies from patients with nonulcer dyspepsia but with normal duodenal mucosa and gastric function were mean 12.0 µmol/1 (SD = 1.7) corrected for the albumin variation 12.0 µmol/1 (SD = 1.5).

3. Findings

3.1 Discussion

The growing fetus accumulates essential elements from the maternal plasma across the feto-maternal membranes in the yolk sac early in pregnancy, later across the placenta. Thus knowledge of plasma or serum zinc variation in pregnancy is essential. A normal weight gain in pregnancy of 10 to 12 kilos entails a need for 300 to 360 mg zinc to be accumulated, if total body zinc is accepted to be just over 2000 mg. the zinc content in food parallels the protein and energy intake, but the bioavailability of zinc is reduced when protein content is low, when phytate and fiber content is high, and when there is competition with, for example, increased amounts of calcium, copper, iron, tin, heavy metals, or chelating drugs. The recommended daily dietary zinc intake in pregnant women was just over 9 mg/day. Thirty-five to forty percent of our daily mean energy intake comes from fat. The saturated fat intake from dairy products is high, as is the calcium intake. Iron fortification of flour in Sweden is a rule; 6.5 mg Fe/100 g is added to sifted flour. The mean intake of magnesium, selenium, and vegetables is also often low[24], [25].

The more pronounced gastric mucosal atrophic lesions are, the more that uptake of essential elements is impaired. Autoimmune atrophic gastritis is a disease that is common and is associated with postpartum thyroiditis and also celiac disease. Celiac disease has a prevalence today of 3 to 4 promille. Women with celiac disease but on a normal diet had a shorter reproductive period and a higher incidence of abortions, stillbirths, and neonatal death than those on a gluten-free diet. A connection between celiac disease, infertility, and fetal malformations in zinc-deficient women has also been shown[26], [27]. The more manifest the proximal duodenal mucosal lesions are, the more often zinc deficiency is found, and the more pronounced is the deficiency. When proximal intestinal mucosal changes develop, zinc deficiency is the first and most evident aberration to appear. When folate deficiency is present, it is almost always preceded by zinc deficiency. Folate uptake from the proximal gut its impaired by zinc deficiency, and it is suggested that folate conjugase, an enzyme that hydrolyzes complex folates to monofolate, is a zinc-dependent enzyme.Bioavailability and uptake of essential nutrients is reuced in patients with intestinal by pass shunt operations. A high frequency of small-for-gestational-age (SGA) infants and congenital malformations has also been registered in women with such shunts. Bioavailability, uptake, and enteral elimination of zinc and other essential element and lipid-soluble vitamins is impaired or increased when malabsorption of lipids takes place resulting in steatorrhea. The fat lost in stools, the lower the serum zinc levels were.

Poorly controlled diabetes with high levels of glycosylated hemoglobin has an increased risk of spontaneous abortion. Higher abortion rates were associated with more advanced White classification. The frequency of abnormal pregnancies and fetal malformations is high in diabetes unless an intensive diabetic treatment regimen is instituted before conception[28].

Renal elimination of zinc is increased in polyuria, for example, from alcohol, thiazids and other diuretic drugs, or from aminoaciduria. Hyperzincuria is documented to occur when there is excessive tissue breakdown. Zinc and other metals could be chelated by oligopeptides and amino acids and eliminated as complexes in the urine. Alcoholic liver disease is associated with low serum-, and granulocyte-zinc levels and hyperzincuria. Some of the laboratory values improved when zinc therapy was given to alcoholics. It is proposed that the diminished maternal zinc levels in alcoholic pregnancies represented the primary mechanism underlying the alcohol-induced fetal dysmorphogenesis. Even a moderate consumption of alcohol during pregnancy is a risk factor spontaneous abortion.

Smoking during pregnancy is associated with a reduction in birth weight, an increase in perinatal mortality, and more frequent spontaneous abortions. Maternal age in it self has no effect on standardized fetal birth weight, but among smokers the reduction in standardized birth weight becomes more pronounced with increasing maternal age. The ratio placental zinc to cadmium is positively related to infant birth weight in pregnant smokers[29]. Increased parity related to increased levels of placental cadmium in smokers and with decreased placental zinc in smokers and non-smokers. The result are consistent with a depletion of body zinc stores with increasing parity and the very long biological half-life of cadmium in the body[30].

Many groups have studied the possible association between maternal and fetal serum zinc concentrations and pregnancy outcome, which was reviewed earlier. A positive association between maternal serum zinc concentration measured early in pregnancy and birth weight was found in a large study. Maternal serum zinc concentration could be used to identify women at higher risk of giving birth to a low-birth weight infant and was a more significant predictor than almost all known risk factors.

Low levels of maternal plasma zinc were associated with mild toxemia, vaginitis, and postdates in the antenatal period. During the intrapartum period, low plasma zinc levels were associated with a prolonged latent phase, a protracted active phase, labor > 20 hours, second stage > 2.5 hours, and cervical and vaginal lacerations. Low levels of maternal alkaline phosphatase were strongly associated with a history of previous stillbirth. It was concluded that a low plasma zinc level is a valid predictor of pregnancy complications and abnormal labor[31].

In a study of plasma zinc and copper concentration and plasma volume in normal pregnancies and women being at risk of delivering a growth-retarded baby, it was found that the intravascular mass of zinc was significantly reduced in the risk group. Another study of zinc and copper concentrations in plasma and urinary zinc excertion compared Hindu vegetarians, meat eaters, and European women. The Hindus had significantly lower zinc levels and higher copper levels, and those who were vegetarians lower protein and zinc intake[32]. Gestation in Hindus was shorter, and their instants were lighter. Low-birthweight and light-for-date infants were much more often registered among the Hindus. It was concluded that no association was found between crude or adjusted birth weight and any of the measures of zinc or copper status in either ethnic group. However, the presence of low-birthweight infants was in fact increased at a rate that was highly statistically significant among Hindus, who had lower zinc intake from food, lowee plasma zinc levels, and higher copper levels, figures that seriously qqueation the conclusion.

The levels of zinc in plasma, erythrocytes, and polymorphonuclear (PMN) and mononuclear (MN) white cells were measured after delivery in women giving birth to babies that were appropriate for gestational age (AGA) or SGA babies. PMN and MN zinc levels were significantly lower in SGA mothers, irrespective of smoking was done after delivery, a stressful situation that alters zinc distribution, as discussed earlier.

Maternal leucocyte zinc concentrations were measured at the beginning of the third trimester of pregnancy and were compared with the weight centiles of their subsequently delivered babies. Early third-trimester maternal leucocyte zinc concentrations were significantly associates with birthweight centiles. Low levels may be used to predict intrauterine growth retardation.

Amniotic fluid zinc levels were significantly lower in cases of mild or severe fetal hypotyrophy compared with normal pregnancies. A positive linear correlation was found between the zinc concentration of amniotic fluid and fetal weight and length. Placental zinc was also lower than in normal pregnancies. No such correlation was found between amniotic fluid zinc concentration and birth weight in another study[33]. The serum zinc concentrations in women whose pregnancies were anencdephalic were significantly lower than in the normal controls. Zinc and

selenium status was assessed in normal pregnancies and in pregnancies with neural tube defects or raised plasma α-fetoprotein, but no detectable fetal abnormality. Significantly lower leucocyteconcentrations of zinc and of selenium were found in the abnormal gestation.
Serum and hair zinc concentrations have been suudied in samples from 29 mothers who gave birth to fetuses with neural tube defects, mainly anencephaly. Mean maternal hair and serum zinc levels were significantly lower thyan in normal controls. Mean fetal plasma zinc was lower and mean hair zinc concentration ws higher than in controls[34]. Increased hair zinc concentration was probably explained by severe deficiency and severely diminished growth of the hair. Maternal zinc deficiency was throught to be one of the factors responsible for neural tube defects.In a study of Chinese women, a strong positive correlation was found between maternal serum, zinc concentrations and birth weight, and a negative correlation was found with zinc level in hair. Congenital abnormality and abortion or low birth weight were not associated with low concentrations of zinc “in plasma or hair”. The conclusions drawn are contradictory to the findings in the study.
In a large population-based study concerning cardiovascular malformations, it was found after adjustment for confounding factors that infants with certain cardiovascular malformations were significantly more likely than were controls to have low birth weight for gestational age.
Abruption placenta was studied in a series of 23,043 consecutive deliveries[32]. The findings were an increased risk of abruption with high parity, and simultaneously a high incidence of unsuccessful pregnancies and premature, undersized, and malformed infants. Major congenital malformations were found in 4.5% of the infants from gestations terminating with abruptyio placenta, compared with an overall incidence of 1.3%, a highly significant difference. In three cases, the infant was anencephalic. A constant relationship between abruption placentae and folic acid deficiency was demonstrated. Abruption occurred in approximately 1% of pregnancies. Hypothetically, women who a\suffer from abruption placentae represent a group of undiagnosed cases of celiac disease.Peripheral placental separation is significantly associated with premature labor and premature rupture of the membranes. The perinatal associated with peripheral placental separation is largely that of prematurity.Premature rupture of membranes (PROM) indicates an increased risk of obstetric complications such as dystocia and perinatal infections. An index from zinc analyses of maternal whole blood, scalp hair, pubic hair, and colostrums was significantly lower in patients with PROM than in patients without. The results suggested that subnormal tissue zinc content in pregnancy might play a role as a causative factor in PROM.
The many findings of signs and symptoms associated with low serum, plasma, leucocyte, monocyte, and amniotic fluid zinc levels in pregnancy make the suspicions of an existing zinc deficiency syndrome more probable, especialy as some of these findings are present in acrodermatitis enteropathica[35]. Positive effects of zinc therapy or dietary changes resulting in increasing serum zinc levels and a reduction of the frequency of maternal and fetal complications would provided the answer. The results from our two randomized studies and the following open-intervention trial were described earlier.In a small supplementation study, 15 mg Zn daily produced an increase in maternal serum alkaline phosphatase. Serum copper levels were changed. In a double-blind study, zinc supplementation was given to low-income, pregnant teenagers. The zinc supplement, 20 mg/day, did not affect mean serum zinc concentrations or hair zinc levels but significantly reduced the number of women with very low serum zinc value late in pregnancy. Supplementation did not affect the outcome of pregnancy, but the incidence of hypertensive disorders of pregnancy was higher in the controls. However, hospital records were lost for 21% of the teenagers. As many as 50% (53/105) of the teenagers gave birth to infants with one or more anomalies. The first visit to the clinic was not made until the 17th week of pregnancy. Thus, the results of the study are difficult to interpret. Pregnant women in a study group of 179 cases received 20 mg zinc aspartate daily. Therapy began between the 12th and 34th week. The control group consist of 345 randomly selected patient next in the birth register of the clinic. Maternal and fetal complications occurred less often in both pregnancy and labor in patients who received zinc therapy. The incidence of small-for-date and large-for-date babies was higher in the control group[36]. Preterm labor and premature separation of the placenta occurred less often in the zinc therapy group.
In a double-blind zinc trial in low-income, pregnant adolescents, 652 subjects were enrolled. Women with < 25 weeks’ gestation were randomized to placebo or 30 mgZn/day as gluconate. Response to zinc was related to maternal weight. Infants of normal-weight mothers given zinc had reduced rates of prematurity and needed assisted respiration less often than controls. Underweight multiparas given zinc had longer gestational lengths than did subjects given the

placebo. Zinc supplementation improved pregnancy outcome in normal-weight women and in underweight multiparas. The zinc group had a positive toxemia screen more often. It was concluded that zinc supplementation was with reduction in premature births and neonatal morbidity.

Another blind, randomized controlled trial enrolled 494 women, mainly of the middle class. Zinc was given as sulphate corresponding to 20 mg Zn daily. Zinc therapy did not change median zinc concentrations in leucocytes, when controlled at the 28-to 32-week visit compared with controls. One case in the zinc group and five cases in the control group ended in spontaneous abortion or were terminated. There were three perinatal deaths in each group. Compliance was just over 50% at 28 to 32 weeks, approaching two-thirds by the time of delivery. It was concluded that zinc supplementation did not seem to offer any benefits no the mother or her fetus. However, because zinc therapy was given irrespective of initial zinc status and complitance was low, the study lost its power. The researchers ought to have included four or five times as many women in order to find a reliable answer. Thustheir final conclusion is probably not relevant.

Finally, another double-blind, randomized trial of oral supplementation was carried out with 22.5 mg zinc daily as citrate in an effervescent preparation. Fifty-six women at risk of delivering a small-for-gestational-age baby received either a zinc supplement or a placebo during the last two trimesters of pregnancy. Zinc therapy significantly reduced the incidence of intrauterine growth retardation, ad most measured indices of labor and health were better in the supplemented group.

4. Conclusion

Zinc is present in and indispensable to all forms of life. Zinc is essential for the normal growth of human beings, and zinc proteins have been shown to be involved in the transcription and translation of the genetic maternal. Zinc deficiency has been incriminated in infertility, abortions, malformations, fetal intrauterine growth retardation, premature and postmature births, perinatal death, and abnormal deliveries with dystocia and placental ablation. Risk groups for developing zinc deficiency, which in turn might modify the expression of the underlying disease, are found among those with insufficient food intake, especially in protein malnutrition; abnormal mucosal uptake, as in celiac disease, abnormal interetinal losses, as in steatorrhae and inflammatory bowel disease.; abnormal renal excretion, as in diabetes with insufficient metabolic control; alcoholism; and treatment with diuretic drugs.Zinc deficiency could be indentified by means of fasting serum or plasma samples or the more laborious estimation of zinc in leucocytes or monocytes if sampling and handling is carefully performed and if stressful situations and acute-phase reactions as fever, delivery, or abortion are avoided.Zinc therapy in identified low-zinc groups has given favorable results and has reduced the frequencies of premature birth, placental ablation, perinatal death, and postmaturity.It is suggested, as we did in 1980, that these data are compatible with the presence of a zinc-deficiency syndrome in pregnancy, which includes increased maternal morbidity, abnormal taste sensations, abnormally short or prolonged gestations, inefficient labor, atonic bleeding, and increased risks to the fetus such as malformations, growth retardation, prematurity, postmaturity, and perinatal death.

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