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# The Role of Zinc in Reproduction

## Hormonal Mechanisms

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## ABSTRACT

Zinc is a very important element in the reproductive cycle of species. In humans, it is necessary for the formation and maturation of spermatozoa, for ovulation, and for fertilization. During pregnancy, zinc deficiency causes a number of anomalies: spontaneous abortion, pregnancy-related toxemia, extended pregnancy or prematurity, malformations, and retarded growth. Delivery is adversely affected by deficiency. These different effects of zinc can be explained by its multiple action on the metabolism of androgen hormones, estrogen and progesterone, together with the prostaglandins. Nuclear receptors for steroids are all zinc finger proteins. Zinc supplementation has already proven beneficial in male sterility and in reducing complications during pregnancy. However, it would be worth conducting larger-scale trials to confirm these beneficial effects.

**Index Entries:** Zinc; hypogonadism; sterility; spermatozoon; testosterone; estrogens; ovulation; fertilization; pregnancy; toxemia; abortion; prematurity; prostaglandins; malformation.

## INTRODUCTION

From fertilization right through to adulthood, humans, like animals, are influenced by a very large number of hormonal factors—true hormones or cell differentiation factors designed to provide for harmonious development. These hormones will affect cell multiplication and differ-

entiation required in the development of organs, and the bone or protein metabolisms responsible for growth before and after birth.

Zinc can act on these hormonal systems as an enzyme cofactor in hormone anabolism or catabolism, by binding to peptide hormones to give them an active spatial configuration, or by modifying the form of these hormones' membranous or nuclear receptors. We intend to examine the effects of zinc and zinc deficiencies on these different stages in life and the hormonal mechanisms involved.

## ZINC AND REPRODUCTION

### *Role in Males*

Severe zinc deficiency has dramatic effects on young, growing male rats since it leads to hypogonadism (*47*). These old animal findings fit what Prasad observed in 1961 and 1963 in terms of the first cases of zinc deficiency in humans (*108–109*). Iranian or Egyptian children from remote villages that practice geophagy suffered from hypogonadic dwarfism; Prasad demonstrated that this was linked to zinc deficiency and could be reversed by giving these individuals zinc. These observations were borne out by other authors in other Middle Eastern villages (*26,59*). Milder zinc deficiency causes oligospermic sterility and impotence in rats and men. This effect has been observed in subjects with drepanocytosis (*1*) and dialyzed uremia (*7,77,95,125*). Abbasi et al. found that oligospermia developed in four out of five volunteers on a restricted 30-wk diet comprising only 4 mg of zinc (*3*). In all these anomalies, supplementation has a beneficial effect and makes male sexual functions return to normal.

Very few studies have sought to establish zinc deficiency in infertile males. Netter et al. (*104*) found low serum zinc in 103 infertile men; the level of serum zinc was correlated to the dihydrotestoterone (DHT) level and not serum testosterone. Zinc supplementation increased testosterone in these subjects together with the number of spermatozoa, and quickly led to pregnancy in some couples. Arver (*9*), studying the sperm of infertile subjects, found an increase in the zinc fraction bound to large molecules in comparison with zinc bound to small-mol-wt compounds. We have studied the seminal fluid of 18 azoospermic subjects who presented a clear reduction in zinc bound to small-mol-wt compounds (ultrafiltrable zinc) in comparison with 47 normal subjects, 40 asthenospermics, and 17 oligospermics; total seminal fluid zinc was identical in all groups (*88*). Zinc treatment of infertility has been successfully performed in 11 oligospermics with a low semem zinc level (*97*), in 10 oligospermics (*63*), in 20 subjects whose sperm presented low motility and low zinc content (*23*), and in 37 oligospermics (*104*).

Male hypogonadism may stem from at least two mechanisms: first an impairment in action of the *Mullerian inhibition factor* (MIS) providing

for testicle differentiation. Budzick et al. (*20*) have shown that this regression was inhibited by zinc. The other zinc-dependent mechanism is both the *synthesis of testosterone* and its activity. In rats (*94*) and in men (*25,77,108*), zinc deficiency has been found to be associated with low testosterone levels (Fig. 1). Furthermore, zinc administration increases the serum level of this hormone in deficient children or adults (*50,63,104,106*). This defective testosterone secretion does not result from a hypothalamus–pituitary gland axis disorder as shown in experiments using rats (*94,113*). However, the response to HCG stimulation is strongly impaired. McClain has shown that HCG stimulation causes 50% less testosterone secretion in deficient rats. Kellokumpu and Rajamiemi observed increased HCG (marked with radioactive iodine) binding on rat testicles following a zinc injection (*80*). Nishi et al. observed that only zinc, contrary to the other metals, enhances the effect of HCG on cyclic AMP and testosterone cell production (*105*). All these studies show the role of zinc in HCG receptor efficiency. Other links exist between zinc and testosterone: 5 α-reductase, an enzyme that converts testosterone into an active metabolite, DHT, is activated by a low zinc intake, but inhibited by an excessive amount (*91*). Congenital 5 α-reductase deficiency is responsible for the absence of external male genitalia, since DTH is indispensible to virilization. Finally, the nuclear receptor of testosterone, like that of all the steroid hormones, is a zinc finger protein, and zinc is necessary for the DHT receptor in the prostate to function (*32*). The different points of zinc action on male hormones are set out in Fig. 2.

Let us note that, conversely, testosterone can modify zinc metabolism: In rats, it leads to an increase in the intestinal uptake of zinc; indeed, methyltestosterone treatment of small-sized children increases their zincemia (*25*). Oligospermia or azoospermia in adults may stem from a lack of response to gonadotrophines leading to testosterone deficiency. The Leydig cells in zinc-deficient rat testicles are smaller and show endoplasmic reticulum abnormalities under electronic microscopy (*66*). Zinc may also be active in the prostate fluid, which contains 500× more zinc than blood plasma. Zinc is linked to certain protein functions and to citrate (*88*). Most zinc is bound to high-mol-wt fractions in seminal vesicle fluid, but to small molecules in prostate fluid (*9*). A prostate fluid protein coding gene was identified in rat prostate that can be induced both by zinc and testosterone (*98*).

## Role in Females

In females, zinc deficiency also triggers sexual malfunctions responsible for reproductive disorders. In mice, mild zinc deficiency leads to a very high number of morphologically or cytogenetically degenerated ovocytes: hypohaploidia or hyperhaploidia (*135*). In rabbits (*116*) or rats (*128*), severe zinc deficiency leads to anomalies in the estrogen cycle or stops ovulation. The same effect has been observed in Rhesus monkeys

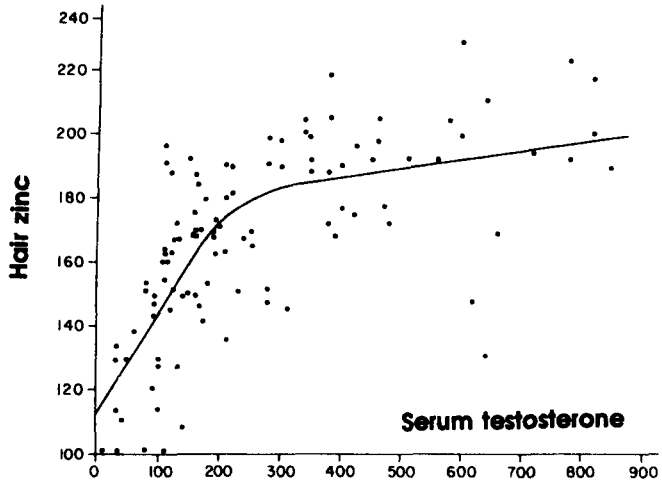


Fig. 1. Relationship between the zinc content of hair (μg/g) and serum testosterone (ng/dL) in 104 small-sized boys between the ages of 10–18 (according to Castro-Magana et al., 1981 [25]).

by Swenerton and Hurley (*129*), who stopped the menstrual cycle by using a purified diet based on soybean protein. Pregnancy cannot occur in deficient animals. A histopathological examination shows that their ovaries contain very few developing follicles and no atresic follicles. In Iran, Ronaghy discovered two women (19 and 20 yr old) suffering from dwarfism with delayed sexual maturation corrected by zinc treatment (*109*). Cavdar et al. found the same symptoms in seven women in Turkish villages practicing geophagia (*27*). Jameson reported extended infertility in zinc-deficient women secondary to coeliac disease (*73*). Soltan and Jenkins, however, measured zincemia in 48 infertile women and found it normal (*122*).

Zinc action on estrogen or progestative hormones has not been the subject of as much experimental research as androgens. However, zinc is indispensable to the function of the mammary gland estrogenic receptor in mice (*118*). It has been proven that the different estrogenic receptors have repetitive cysteine sequences that make them function like zinc finger proteins (*86*). The action of these receptors is outlined in Fig. 3. Bunce and Vessal have shown that zinc-deficient rats present reduced estrogen sensitivity in the absence of any modification in the number of receptors (22). However, there is an increase in the number of receptors in the cell nucleus, hence, perhaps their inability to bind to their gene. It is worth mentioning that copper promotes estrogen binding to their protein receptor in the cytosolic compartment (*45*). The same effect occurs with progesterone, whose receptor functions according to the same model. Lohmar and Toft have shown that zinc is necessary in hen oviduct receptor functions (*93*).

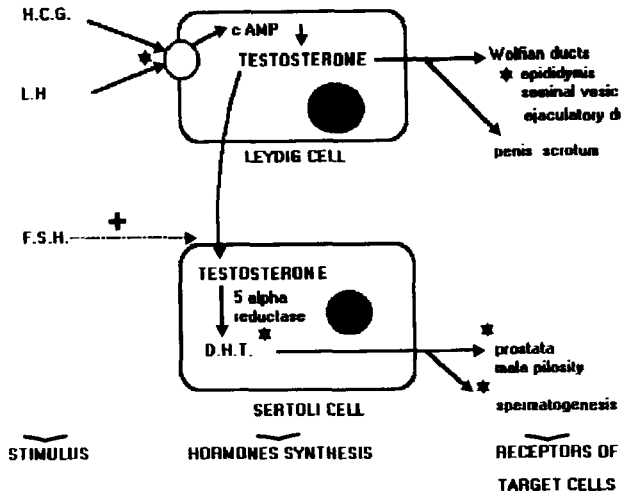


Fig. 2. Zinc and androgen hormone metabolism (the zinc-dependent mechanisms are marked with an *).

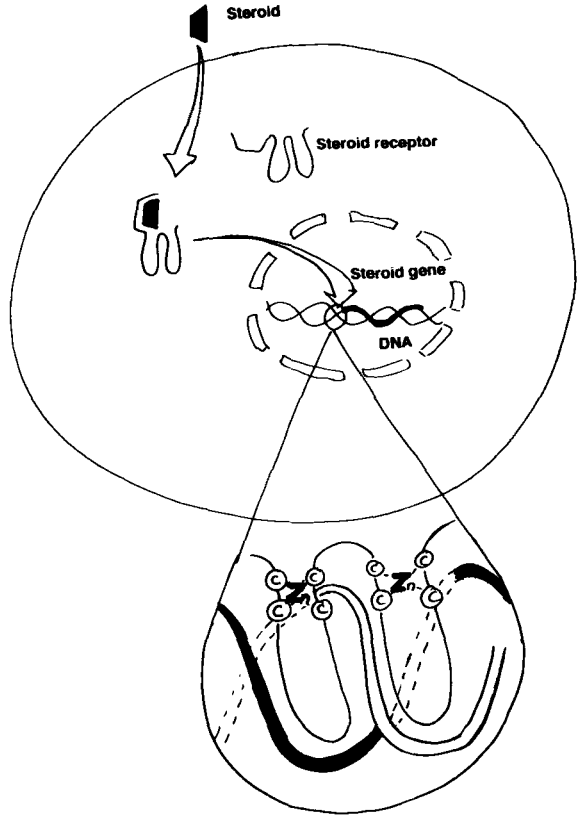


Fig. 3. Functional outline of a steroid hormone nuclear receptor showing its zinc fingers interleaved with DNA and providing for the expression of the corresponding gene.

## ZINC AND PREGNANCY

### *Zinc Requirement of Pregnant Women*

Zinc requirement can be estimated according to the amount contained in tissues appearing during pregnancy (fetus, placenta) plus the fluids lost during delivery. The quantity of zinc required is 100 mg (84), that is, 3% of the mother's total zinc. This accumulation of zinc is progressive and very important in the last quarter. Shaw has calculated that the fetus builds up 249 μg/Kg/d, that is, 0.21 mg/d at 24 wk opposed to 0.67 at 36 wk (*117*). On the basis of these calculations, there is an estimated additional requirement of 0.75 mg/d toward the end of pregnancy. In light of an average estimate of 20% zinc bioavailability in food, a WHO expert committee has estimated that the food requirement in women increases from 11 to 15 mg/d during pregnancy (*5*). The lack of menstruation spares only very little zinc (0.01 mg/d), whereas urinary losses increase by 0.4 mg/d as of the end of the second quarter.

### *Zinc Deficiency During Pregnancy*

Biological markers should, in theory, make it possible to answer the question: Does pregnancy lead to zinc deficiency? Unfortunately, the use of these markers, difficult and controversial enough in normal adults, becomes all the more chancy during pregnancy owing to hemodilution, hormonal variations, enzyme content modifications, and changes in the protein metabolism.

Nearly all researchers found a drop in serum or plasma zinc during pregnancy (*14,39,60,62,70,102,110*). This drop is very rapid until 35 d after ovulation; after a slight increase up to day 55, the reduction is regular until term (*15*). Serum levels at term are 10–30% lower than levels before pregnancy, but in certain studies, larger drops are described. Ghosh et al. found a 60% drop in China, which may reflect low reserves in the Chinese population (*52*). There is no doubt that this drop is the result in part of hemodilution, but also of the drop in albumin levels, which, in plasma, is the main vector (*70*). It is very difficult to know whether a redistribution of zinc takes place during pregnancy, since the few studies on this subject diverge (*44,127,137*). Several authors found even lower serum zinc at the end of pregnancy in women with a low socioeconomic status (*28*) or vegetarian women who have low, poor bioavailability intakes (*24,138*). For Adeniyi, maternal serum zinc is inversely correlated to leukocyte and placenta zinc owing to privileged transfer to these tissues during pregnancy (*4*). Zinc supplementation has only a weak effect at the end of pregnancy (*62,69*). During the first quarter, however, serum zinc increased after supplementation (*15,62*). The serum zinc level, therefore, drops under the influence of factors other than zinc intake, but insufficient intake does aggravate this drop.

Most experts consider that a level of 40 μg/100 mL (*62*) or 55 μg/dL (*70*) constitutes the threshold of a "normal" end-of-pregnancy drop.

When considering zinc concentration in hair, a few authors found that pregnancy does not affect this indice (*62,127*). Several authors, however, describe a gradual reduction (*16,52,60,69,133*). In Ghosh's study, the level drops from 182 ± 31 before pregnancy to 158 ± 19 μg/g by delivery.

When leukocyte zinc was considered as an indice of zinc status, Simmer et al. (*119*) only found a nonsignificant drop in PMN zinc at delivery, whereas Meadows et al. (*99*) found a close correlation between leukocyte and muscular zinc in pregnant women. Raja (*111*) found a far lower level at the end of pregnancy in PMN cells. Indeed, Meadows et al. (*100*) showed that maternal leukocyte zinc was correlated to fetus leukocyte levels and dropped during pregnancy.

Although an analysis of amniotic fluid zinc can only serve to compare groups of pregnant women, it is worthwhile since the level may increase in certain malformation-producing pathologies, no doubt as a result of an increase in the zinc-rich α-fetoprotein level (*14*). The amniotic fluid contains a small amount of zinc, estimated in this author's experiments (*39*) to be 20 ± 11 μg/dL; samples will thus be highly sensitive to contamination when collected or to presence of meconium. A very sensitive method is therefore required, hence the discordant levels of certain authors. Furthermore, the level will increase considerably in the presence of meconium and cells, which may explain the rise in the mean value noted during the last weeks of pregnancy (*114*). Certain authors found a lower amniotic fluid level when the fetus was male (*89*).

In conclusion, a marker, such as leukocyte zinc, indicates a drop in the zinc content of maternal tissues. This is confirmed by a larger reduction in serum levels than expected as a result of hypervolemia and hypoalbuminemia, and by a reduction in zinc levels in hair found by most authors. This drop is consistent with the additional requirement owing to the placental and fetal tissues (+5 mg/d toward the end of pregnancy) that are not covered by additional dietary intake or enhanced intestinal absorption rates. Indeed, Turnlund (*131*), using stable isotopic zinc load tests, and Statter et al. (*126*), using normal zinc loads, found no increase in intestinal absorption. Statter et al. even found zincemia following the load lower in women during delivery. The additional requirements of fetal tissues are thus covered from the maternal tissues; yet it has been shown that, in rats (*78*), the transfer from maternal tissues to fetal tissues is not optimal unless the mother is in a state of protein catabolism and is problematic if she is in a state of anabolism.

## *Impact of Zinc Deficiency on Pregnancy and the Mother*

Given the multiple biological roles of zinc, it is not surprising that deficiency can upset the process of gestation. The hormonal upsets

caused by this deficiency are worth stressing: drop in corticosterone, the release and transport of estrogens, prostaglandin synthesis, increase in progesterone. Moreover, zinc deficiency leads to anorexia or a reduction in food intake, which in itself has serious consequences (*5,8,71,76*).

### *Spontaneous Abortion*

During the first quarter, Breskin et al. (*15*) found an abnormally low level of zinc in 7 of the 25 subjects who had a spontaneous abortion. Ghosh et al., however, found no reduction in the serum zinc level of 69 women aborted between the 8–16th wk (*52*). Nonetheless, it is worth noting that experimental zinc deficiency triggers a drop in uterine fluid zinc, which is thought to be the early source of zinc intake for the ovum (*49*). This mechanism might explain the constant increase in abortions in Rhesus monkeys (*54,129*). Also, prostaglandin synthesis disorders resulting from zinc deficiency may play a role, since Dib and Carreau (*34*) observed reduced abortion and mortality by supplementing zinc-deficient pregnant rats with γ linolenic acid. One should note, on the contrary, that an excessively large amount of zinc seems to foster early resorption (*87*).

### *Hypertension and Toxemia Pregnancy*

Several authors found a drop in maternal serum zinc (*11,30,56,82*) or placental zinc in preeclampsia (*18*), sometimes associated with a reduction and sometimes with a rise in serum copper. Zimmerman showed that five women developing preeclampsia during the third quarter had lower serum zinc between the 6–14th wk of amenorrhaea (*138*). For Lazebnik et al. (*90*), the frequency of moderate pregnancy-related toxemias was 5.6% in women, with low serum zinc, as opposed to 0.7% in women with normal serum zinc. Adeniyi (*4*) only observed a drop in maternal leukocyte zinc when the child presented a low birthweight; in this case, placenta and umbilical cord zinc and estradiol were also lower. Paradoxically, maternal serum zinc was higher in this group. Although the mechanism has not been proven, this effect is not surprising, since in other circumstances, zinc deficiency is associated with an increase in blood pressure. Zinc action may entail a modification in hormonal secretions (estrogens, prostaglandins), but this trace element furthermore modulates the activity of the angiotensin converting enzyme. Whatever the mechanism may be, there is a direct link with zinc status, because Hunt et al. observed only 2% pregnancy-related hypertension in women receiving a 2-mg zinc supplement as opposed to 16% in women receiving a placebo ($p < 0.003$) (*69*). On the contrary, a larger number of biological signs of toxemia have been observed in zinc-supplemented women without this having any impact on the course of pregnancy or the newborn in double-blind supplementation trials (*31,96*). This zinc preeclampsia link should be related to the possible consequences of preeclampsia for the newborn (reading and learning disorders, hyperactivity, epilepsy) (*18*).

These pathologies are found in experimental zinc deficiency or associated with a drop in serum zinc, such as in fifth-day convulsions.

### *Other Complications During Pregnancy*

Women with refractory anemia during pregnancy had lower serum zinc (*73*). This finding is of course isolated, but to be compared with the microcytic anemia noted in Rhesus monkeys subjected to very marginal zinc deficiency (*53*). Other complications can perhaps be linked to zinc deficiency. Thus, Mukherjee et al. (*102*), found, together with a low serum level during the second and third quarter of pregnancy, a larger number of maternal infections, fetal distress, and tissue fragility. The frequency of Candida-related vaginitis increased in pregnant women with lowered zincemia. Furthermore, experimental zinc deficiency reduces glucose tolerance both in male rats (*38*) and pregnant rats (*124*). It would therefore be interesting to see whether the drop in glucose tolerance found during pregnancy is linked to zinc deficiency or not.

### *Length of Gestation*

Zinc deficiency is associated with both prematurity (*74*) and prolonged pregnancy. Prolonged pregnancy is noted in experimental deficiency in rats (*21*) and might be owing to an increase in the progesterone over estrogen ratio (*8*). Favier (*39*) found a relationship between maternal zinc on delivery and the length of gestation. Cherry et al. (*31*) reduced the number of cases of prematurity by giving pregnant women a zinc supplement. Several studies showed a link in pregnant women between an abnormally low serum zinc level (*74,90*) or lowered amniotic fluid zinc (*6*) and an abnormal length of pregnancy. Finally, Jameson noted a drop in postmaturity in pregnant women given a 45 mg/d zinc supplement.

### *Complication During Delivery*

Zinc deficiency upsets delivery in numerous ways in animals: excessive loss of blood and increased stress (*8*). Complications during delivery are found in primates (Rhesus monkeys) who are subjected to only a mild deficiency (*54*). Jameson (*73*) found, in several studies, lowered serum zinc in early pregnancy in 18 women with complications pertaining to length of labor or atonic bleeding during delivery. McMichael (1982) found increased bleeding in mothers with low zincemia (*5*). Lazebnik et al. noted a very significant increase in the prelabor phase and, above all, the period of dilatation in zinc-deficient women (*90*). Finally, 45 mg/d zinc supplementation reduced the frequency of abnormally long labor (*75*).

### *Postpartum Consequences*

Zinc status slowly returns to normal after delivery. Serum zinc increases, but 9 wk after delivery remains below the initial level (*110*). Moreover, breast feeding is another condition in which the woman will

dip into her reserves to provide zinc in breast milk. In rats, zinc deficiency reduces not only the total production of milk, but also its zinc content. This effect may be explained by the link between zinc and prolactin, and by the lower increase in the level of RNA in mammary tissue where it is required to make quantities of casein (*103*). In humans, although several studies did not find a link between dietary zinc intake or the mothers' status and level of zinc in milk (*84*), Krebs (*85*) et al. did note a slow down in zinc level reduction in milk in zinc-supplemented women during pregnancy and breast feeding.

### *Consequences for the Fetus and Newborn*

The consequences of the zinc deficiency are equally diverse for the newborn, ranging from prematurity and low weight to even malformations. They may even extend to the period well after birth. Mukherjee et al. (*102*) noted that, when the mother had a low zinc level during the first quarter, the newborn had a low Apgar score. The effect of zinc on fetal growth will be examined elsewhere.

Severe zinc deficiency cannot be brought about before fertilization, since it stops the estrogen cycle and leads to absence of fertilization. Triggered the first day after fertilization, it leads to a very high percentage of bone, nervous, ocular, or pulmonary malformations. Even when it is only triggered for 3 d (from the 10th to the 12th day), it leads to cerebral malformations (*78*). The effect is very rapid and becomes apparent as of the third day on fertilized eggs. This can be explained by the ovum's dependence during the first few days on the uterine fluid as a source of zinc, and the zinc content of this fluid is lower in deficient states. The zinc-dependency of this effect has been proven using embryo cultures in a zinc-deficient medium, which showed a large number of malformations, whereas the addition of zinc to the medium leads to normal development (*101*).

The main teratogenic manifestation of zinc deficiency seems to be a defective closing of the neural tube (spina bifida or anencephaly). The hypothesis put forward by Sever and Emanual (*115*) whereby one origin of spina bifida was linked to zinc deficiency was based on the coincidence between regions of the world where this anomaly was most frequent and regions with a high prevalence of zinc deficiency. Since numerous studies have borne out this hypothesis (Table 1), the studies on the zinc status of mothers of children with neural tube defects (NTD) have shown there is disturbed zinc status in comparison with the mothers of healthy children. By using newborn fibroblast cultures, we were able to show that the speed of uptake of radioactive zinc was lower in children with NTD (*42*). Our results confirmed those of Zimmerman, which concerned only three cases (*138*). We showed that the defect was not the result of the total absence of a carrier, but perhaps of a nonopti-

mal structure. This defect manifests itself differently according to the zinc content of the culture medium.

Many studies have been made and many hypotheses put forward to explain this effect (*35,78,79,112*). Zinc deficiency reduces the activity of numerous enzymes in the brain: thymidine kinase, 2'3' cyclic nucleotidyl phosphorylase, lactate dehydrogenase, L-glutamate dehydrogenase. It may lead to a stop in cell multiplication at a crucial period in morphogenesis. Zinc may be involved in the expression of certain genes through the zinc finger protein mechanism, a small number of which have already been identified, such as the retinoic acid or steroid receptors (*64*). One of these zinc finger proteins, Egr-1, has been singled out as acting in parallel with C-Fos protein triggering the proliferation and differentiation of fibroblasts and epithelial cells. Zinc is also necessary in many cell differentiation factors, NGF, and gustin. Zinc deficiency also upsets the cytoskeletal assembly of brain cells (*107*). The speed at which cells travel is also partly conditioned by this phenomenon and plays a considerable role in tissue movements during embryogenesis. Finally, some authors have presumed that the teratogenic effect of zinc was owing to a hyperproduction of free radicals that are liable to damage DNA.

Zinc deficiency potentiates the effect of many teratogenic drugs in animals, either compounds that can chelate zinc, such as EDTA or penicillamine (*79*), or drugs not known as chelators, such as 6 mercaptopurine (*68*), thalidomide (*72*), salicylate (*83*), acetazolamide (*55*), or valproate (134). The teratogenic effect of alcohol is also enhanced by zinc deficiency in rats (*81*). Alcoholism leads not only to zinc deficiency, but also an inhibition of the placental transport of zinc (*51,136*). Zincemia is abnormally low in newborns with fetal alcoholic syndrome (*10,46*). Diabetes malformations may be the result of secondary zinc deficiency: A lower zinc content was found in diabetic rat fetuses (*37*). The administration of zinc to pregnant diabetic rats improves the weight of the fetuses and their ossification (*132*).

If one examines the effect of gestational zinc deficiency in animals, one can see that the functioning of several organs is also upset after birth: Test learning and memorization difficulties have been discovered in babies born of zinc-deficient animals (*57,58*). These findings are to be put together with those of other researchers on the effect of zinc deficiency during the first weeks of life when a drop in neurons has been noted (*48*). The immunity of mice born of mothers fed 5 ppm of zinc is abnormal for 6 mo (drop in Ig2A and IgA) even when the baby mice are fed normal diets as of birth. In the event of greater deficiency, the animals are not able to form rosettes after immunization (*12*). Also, transient hypogammaglobulinemia in the newborn may be owing to gestional zinc deficiency (*92*). Indeed, this anomaly is very often associated with mental retardation or malformations that zinc deficiency also creates in animals.

Table 1
Links Found by Different Authors
Between Maternal Zinc Status and the Occurrence of Defective Neural Tube Closure in the Newborn

| | *n* | Zn mg/d | Biological effect | Clinical effect | Side effect |
|---|---|---|---|---|---|
| Hambidge et al., 1983 (*62*) | 10 | 15 mg | ⇧ Serum Zn mother early pregn. no effect end pregn. ⇧ saliva, hair zinc, PAL | | |
| Breskin et al., 1983 (*15*) | 5 | 15 à 25 mg | ⇧ Serum Zn mother early pregnancy | | No |
| Hunt et al., 1984 (*69*) | 107 | 20 mg | Less women with Zn <53 μg/L | Decrease toxemia | No |
| Taper et al., 1985 (*130*) | 24 | 10 mg at 20 wk during 4 wk | No effect serum Zn ⇧ Zn retention | | |
| Jameson, 1976 (*74*) | (7) | 90 mg | | ⇩ Labor duration ⇩ bleeding | No |

| | | | | | |
|---|---|---|---|---|---|
| Jameson, 1982 (*75*) | 64 | 45 mg | | ⇩Postmaturity<br>⇩prolonged labor | No |
| Jameson, 1982 (*75*) | 3 | 60 mg | Low Zn before pregn.<br>⇧serum Zn<br>⇧RBP | | |
| Cherry et al., 1989 (*31*) | 556 | 30 mg or placebo | | ⇩Normal W mothers prematurity<br>Under W. primipara no effect<br>Under W. multipara<br>⇩⇩gestation<br>Variance of factor for height | ⇧Biological risk of toxemia |
| Kynast, 1986 | 179 | 20 mg 12–34 wk | | ⇩Complications<br>⇩LBW<br>(compared to 345 un-supplement) | |
| Mahomed et al., 1989 (*96*) | 494 | 20 mg at 20 wk or placebo | No ⇧ of leuco ZN | No difference on BW APGAR, pregnancy, or delivery | ⇧Biol. risk of toxemia |

### Effect of Supplementation During Pregnancy

Although a limited number of women have received supplementation to date, it is worth noting that, although certain studies find no beneficial effect, a number of others record an increase in zincemia around the 15th wk, a drop in the number of pregnancy-related toxemias, a reduction in the length of bleeding, extended labor, or postmaturity (Table 2). However, no statistical information can be drawn on the possible preventive effect of malabsorption owing to the small number of women treated. The effective dose seems to be between 20–40 mg/d.

### Zinc-Dependent Hormonal Mechanisms During Pregnancy

During the first weeks of pregnancy, estrogens and the 17 OH progesterone of the corpus luteum play a prime role in maintaining nidation. The HCG hormone plays an important role in maintaining the corpus lutium. As of the 10th wk, the role of HCG decreases, and the large quantity of estrogen and progesterone produced comes from the placenta. Other hormones play an important role, such as HPL, a hormone close to prolactin, but of placental origin and endowed with somatotropic properties. The role of zinc in terms of HCG receptor sensitivity or the action of estrogen and progesterone hormones on their respective receptors has been described elsewhere. However, the effect of zinc on these hormones has been little studied during pregnancy.

The triggering of labor is a complex process activated by prostaglandins, but inhibited by progesterone. A sudden drop in progesterone levels is normally set in motion by the induction of an ovarian enzyme, 20-α hydroxysteroid dehydrogenase, which transforms progesterone into an inactive derivative. Zinc deficiency in gestating rats considerably slows the drop in progesterone levels and leads to a delay in the induction of 20-α OH steroid dehydrogenase (*21*). PGF2 prostaglandin may participate in the induction of this enzyme.

Zinc has many mechanisms capable of influencing the formation of prostaglandins. It protects polyunsaturated fatty acids from peroxydation; it is the cofactor of Δ-5 and Δ-4 desaturase enzymes. Conversely, PGE2 prostaglandins stimulate the absorption of zinc, whereas PGF2 fosters its excretion, at pharmacological doses. During pregnancy, the prostaglandins most involved in delivery are PGE2, which promote the secretion of relaxin by the uterus, providing for dilatation of the cervix, and PGE2 and PGF2, which trigger the uterine contractions required for delivery. The plasma level of PGF2 is lower in zinc-deficient rats (*123*). Cunnane et al. (*33*) noted the disappearance of uterine contractions, and a drop in the utero-placental flow linked to a reduction in PGE2 and

Table 2
Effect of Zinc Supplementation During Pregnancy

| | |
|---|---|
| Sever and Emanual, 1973 (*115*) | Hypothesis of zinc deficiency as a cause for NTD |
| Hambidge et al., 1975 (*61*) | 7 Mothers with Acrodermatitis: 2 malformations |
| Jameson, 1976 (*74*) | 234 Pregnant women: on 8 malformations, 5 mothers ↘ serum zinc |
| Prasad, 1979 (*108*) | Geographical area in Middle East identical for zinc and anecephalia |
| Cavdar et al., 1980 (*26*) | 10 Mothers of anencephali ↘ serum zinc |
| Bergman et al., 1980 (*13*) | 17 Mothers of spina bifida, ↗ hair zinc |
| Soltan and Jenkins, 1982 (*121*) | 54 of children with malformations (18 NTD) ↘ mother's serum zinc |
| Favier et al., 1983 (*40*) | 540 Deliveries: 1 hydrocephalus ( ↘ mother's serum zinc) |
| Buamah, 1984 (*19*) | ↘ Serum zinc in mothers of 15 anencephali |
| Zimmerman, 1984 (*137*) | ↘ Zinc α-2 macroglobulin/albumine in 4 mothers with NTD |
| Favier et al., 1987 (*41*) | ↘ Serum zinc 23 mothers of spina bifida |
| Cavdar et al., 1988 (*29*) | ↘ Serum and hair zinc in 29 mothers of anencephali in Turkey |
| Hinks et al., 1989 (*67*) | ↘ Leukocyte zinc 6 mothers of spina bifida and 16 mothers with ↗ α fetoprotein in blood |

PGF2 prostaglandin synthesis in the uterine tissue in zinc-deficient gestating rats. These results agree with Simmer and Thompson's (*120*) finding of a correlation, in pregnant women, between the zinc content of monocytes and their PGF2 content.

## CONCLUSION

All the hormones involved in reproduction and development are sensitive to zinc status often by several mechanisms. So it is not surprising to find as many effects of zinc deficiency on all the stages of development of the newborn. Moreover, it is during pregnancy and growth that more net effects of zinc supplementation have been found. We have now to achieve more, large double-blind supplementation studies to verify that it is efficient and harmless (in our opinion, with zinc associated with some other micronutrients to prevent interaction in different metabolisms), and certainly in a few years, this practice will be as common as iron supplementation.

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