

REPORT ON THE INFLUENCE OF HEAVY METALS ON THE EVOLUTION OF THE PREGNANCY IN SMOKING MOTHERS

Bara Lucian*, Bara Camelia, Bara Vasile, Micle Otilia, Mureșan Mariana

**University of Oradea, Faculty of Environmental Protection, 26 Gen. Magheru St., 410048 Oradea, Romania e-mail: baralucian@yahoo.com*

Abstract

Cadmium, a toxic heavy metal, has been incriminated in the etiology of essential hypertension. Zinc an essential micronutrient necessary for growth, competes with cadmium for binding sites in biochemical processes; zinc deficiency states might expose an individual to increased risk of cadmium toxicity. The increased sensitivity to cadmium during pregnancy could also be related to the effect of progesterone on zinc and cadmium metabolism through the actions of metallothione (MT). Several studies in lab animals have documented a late gestation drop of maternal MT levels. This thought to be due to rising progesterone levels. If there is also a late gestation drop in human maternal MT, then the propensity toward maternal cadmium toxicity would be enhanced. Therefore, we propose that when a zinc deficient woman becomes pregnant and is exposed to both the nutritional demands of the fetus and to the influence of progesterone, she will be likely to develop the manifestations of cadmium toxicity.

Key words : heavy metals, smoking mothers, pregnancy.

INTRODUCTION

For any theory of the etiology of toxemia to be acceptable, it must explain the many finding of the disease. Included is the high incidence of toxemia in the young primigravida, in twin pregnancies, and in women on a low income diet.

The familial tendency to develop toxemia, the increased incidence as term is approached, the decreased incidence with a subsequent pregnancy, and the uniqueness of the disease to the human race should also be explained. Furthermore, the occurrence of hypertension, proteinuria, edema, vasospasm, vasculitis, fetal growth retardation, and the additional pathophysiology seen in toxemia requires an explanation.

Finally the crucial role of the placenta in the etiology of this disease demands an explanation, since toxemia does not characteristically develop in the absence of placenta. This hypothesis attempts to address these questions.

MATERIAL AND METHOD

The role of zinc

Zinc is a mineral necessary for growth primarily because of the zinc dependent enzyme thymidine kinase. It has been determined that most of adult diets supply 12-15 mg Zn / day. The recommended daily allowance for pregnant women is 20 mg Zn/day, so the increased likelihood of zinc deficiency during pregnancy is evident.

During normal human pregnancy, plasma zinc levels fall. Presumably, this decrease partly reflects the uptake of zinc by the fetoplacental unit. This correlates with the fact that during pregnancy, maternal physiology adjusts to assure the fetus of the proper amounts of nutrients necessary for growth and development. Because the fetus grows rapidly in the last two months of pregnancy, a three fold increase in the need for zinc occurs in the later stage of pregnancy.

Three studies have shown significantly lower serum or plasma zinc levels in women with severe toxemia when compared to levels in women with normal pregnancies at the same stage of gestation. In a recent study, women who ultimately experienced hypertension/toxemia were found to have low plasma zinc levels early in pregnancy.

Manifestations Common to Toxemia of Pregnancy and Zinc Deficiency in Laboratory Animals are: Abnormal water balance, elevated hematocrit, altered prostaglandis, decreased immune competence, bleeding tendency, abnormal platelet aggregation, and growth retardation

Zinc and cadmium are in the same subgroup of the periodic table so they are physically and chemically similar. It is likely that zinc deficiency potentiates possible toxic effects of cadmium, since zinc and cadmium are regarded as antimetabolites of one another. The concept of isomorphous replacement of metals maintains that those metals whose physicochemical properties are similar might act antagonistically in biological systems. In the light of possible zinc/cadmium interactions, it should not be surprising that the young, the pregnant, and those on a low protein diet are more susceptible to zinc deficiency and resultant cadmium toxicity.

The Role of Cadmium

As early as 1955 it was found a forty-fold excess of urinary cadmium in untreated hypertensive. Furthermore, high serum cadmium was found in hypertensive when compared to controls. The strongest evidence

linking cadmium with hypertension comes from animal studies. In laboratory animals, hypertension has been produced in several experiments by exposure to cadmium. Most interesting is the fact that in 1965, an experimental model of toxemia was developed in pregnant rats injected with cadmium salts. The presence of functioning placental tissue seemed necessary for cadmium toxicity to be manifested.

Cadmium toxicity may be monitored through analysis of beta 2-microglobulin in plasma and urine. Interestingly, a recent article has advocated analyzing urine for beta 2-microglobulin in order to diagnose toxemia in its early stages. Furthermore, other studies have found statistically significant elevated levels of beta 2-microglobulin in groups of preeclamptic women when compared to levels in normal pregnant women. These findings may reflect cadmium toxicity in human pregnancy induced hypertension.

A review of the effects of cadmium toxicity shows a striking resemblance to many of the manifestations of toxemia.

Hypertension, proteinuria, altered water metabolism, fetal growth retardation, sodium retention, reduced placental perfusion, placental infarcts, altered prostaglandins, direct vasoconstriction, inhibition of energy metabolism in the cardiovascular system, decreased immune-competence, increased vascular response to adrenergic stimulation, pulmonary edema, convulsions, arteriolitis, liver injury, renal lesions.

How might cadmium cause hypertension was summarized the effects of cadmium in laboratory animals that may relate to the etiology. These include vasoconstriction, sodium retention, altered catecholamine metabolism, increased rennin activity levels, and inhibition of energy metabolism in the cardiovascular system.

The role of metallothionein

The hypothesis that cadmium toxicity plays a role in the etiology of toxemia becomes more plausible in the light of what is known about metallothionein (MT). MT is a low molecular weight sulfhydryl-rich protein believed to function in the detoxification of cadmium and in zinc homeostasis. It is produced primarily by the liver and is analogous to ferritin in iron metabolism.

The synthesis of MT is apparently under hormonal control, since glucocorticoids stimulate its synthesis and progesterone inhibits this response. Considering the humoral roles of the placenta and the fetal adrenal, dramatic changes in MT synthesis during pregnancy might be expected. As anticipated, a recent study in rats has shown a four fold increase in fetal hepatic MT synthesis when compared to normal adult levels. MT may serve to either ensure adequate storage of zinc for fetal development or protect the fetus against metal toxicity.

More relevant to this discussion is the fact that a five fold decrease in maternal hepatic MT synthesis was demonstrated in late gestation. The decrease was attributed to rising progesterone levels in the later stages of pregnancy. Two additional studies have also shown a late gestation drop in maternal MT levels.

If there is also a late gestation drop in human maternal MT levels, then the propensity toward maternal cadmium toxicity would be enhanced. Because progesterone is incriminated, gestational hypertension might be expected in other animals. The human placenta, however, does not rapidly metabolize progesterone into less active compounds as do the placentas of other species.

Zinc deficiency states seem to inhibit the accumulation of MT, reflecting this is the fact that the half-life of MT is reduced in zinc deficient animals.

A third factor affecting MT synthesis may be genetic. In certain strains of laboratory animals, an increased sensitivity to cadmium toxicity has been demonstrated. It appears that in these susceptible animals, the degradation of MT is increased. This genetic tendency towards cadmium toxicity may correlate with the familial tendency to develop toxemia.

The role of progesterone

The human placenta produces progressively larger amounts of progesterone during the course of pregnancy. Also the human placenta, of all studies, is metabolically unique in that progesterone is not rapidly metabolized into less active metabolites.

These findings parallel the observations that gestational hypertension is only seen in humans, and that toxemia usually occurs in the latter part of pregnancy.

In a study of 1,050 women using depo-medroxyprogesterone for contraception, 8.3 percent experienced significant elevations in blood pressure. In addition, progestogens have recently been incriminated in the etiology of hypertension induced by oral contraceptives.

Likewise, the higher levels of progesterone in twin gestations correlate with the increased incidence of toxemia in this condition.

Some studies were able to induce hypertension in male rabbits using progesterone.

The renal glomeruli showed changes similar to those which have been described as specific to preeclampsia. Similar lesions have also been produced by cadmium exposure in rats.

We suspect that the effect of progesterone on zinc and cadmium metabolism. Progesterone inhibits the cellular uptake of zinc and, as noted above progesterone inhibits the accumulation of MT, thus reducing cadmium detoxification. This hormonal effect, we believe, explains the

crucial role of the placenta in the etiology of pregnancy induced hypertension.

RESULTS AND DISCUSSION

The decreased incidence of toxemia in cigarette smokers has been difficult to explain. However, tobacco represents a significant source of cadmium, we theorize that this preliminary dosing with cadmium confers some protection against a later exposure to cadmium during pregnancy. We base this on the fact that in laboratory animals pretreatment with cadmium or zinc is known to protect them against a subsequent usually toxic dose of cadmium. As both pretreatment cations stimulate the synthesis of either zinc or cadmium metallothionein (MT), protection against the acute effects of cadmium has been attributed to these metal binding proteins. Furthermore, Webb found that the synthesis of MT, when induced by an initial exposure to zinc, is stimulated rapidly and without lag on subsequent administration of cadmium.

We feel that the increased risk of toxemia in the primigravida without previous excessive cadmium or zinc exposure might also be related to this phenomenon. Having gone through the first pregnancy and its associated cadmium exposure, the mother accommodates a subsequent pregnancy more efficiently by producing MT without lag.

It is evident that the susceptibility of animals to cadmium toxicity is influenced by a wide variety of factors. Probably of greatest importance is the effect of nutrition on cadmium metabolism since deficient dietary intakes of several nutrients besides zinc can greatly exacerbate the severity of cadmium toxicosis. Also, the absorption of an oral dose of cadmium is two times greater in iron-deficient rats than in controls.

CONCLUSIONS

We hypothesize that zinc deficiency states associated with pregnancy and a low protein diet might confer an increased sensitivity to cadmium toxicity. The increased sensitivity to cadmium during pregnancy could be due to two factors. First, shunting of zinc and other minerals to the growing feto-placental unit might induce a maternal deficiency.

Second, the high levels of progesterone produced by the placenta could inhibit metallothionein accumulation and free previously bound cadmium. Thus, when the biologically available cadmium/zinc ratio increases, then cadmium induced vasoconstriction, sodium retention, altered catecholamine metabolism, and increased rennin activity may occur with resultant hypertension.

According to our hypothesis, the following measures would reduce the incidence of toxemia:

1. high protein diet;
2. zinc supplementation of diets high in refined grains, since zinc is lost in the refining process.
3. Iron and calcium supplements are also important.

The hypothesis might be tested by supplementing diets in populations prone to toxemia who subsist to a large degree on refined grains. If this policy is instituted, we feel that metallothionein production will be stimulated prior to pregnancy, and, as a consequence, more efficient protection against toxemia will result.

Supporting this hypothesis is the fact that Hamlin was able to virtually eradicate eclampsia and severe preeclampsia in a population prone to toxemia by early and constant education in the principles of a high protein diet and by reduction of refined carbohydrate intake. In essence, these patients were instructed to visit the butcher and avoid the baker. Related is the fact that 20 mg of zinc required per day in pregnancy is difficult to meet unless the diet contains some type of animal protein.

Considering the evidence, we anticipate that research on metallothionein in normal and abnormal pregnancies will reveal a role for cadmium in the etiology of pregnancy induced hypertension. Hopefully, the importance of adequate zinc nutrition prior to and during pregnancy will be recognized by nutritionists, obstetricians, pharmaceutical companies, and the producers of refined carbohydrates.

REFERENCES

1. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002;99:159-167.
2. Banerjee S, Chambers AE, Campbell S. Is vitamin E a safe prophylaxis for preeclampsia? *Am J Obstet Gynecol* 2006;194:1228-1233.
3. Belizan JM, Villar J. The relationship between calcium intake and edema-, proteinuria-, and hypertension: an hypothesis. *Am J Clin Nutr* 1980;33:2202-2210.
4. Clausen T, Slott M, Solvoll K, Drevon CA, Vollset SE, Henriksen T. High intake of energy, sucrose, and polyunsaturated fatty acids is associated with increased risk of preeclampsia. *Am J Obstet Gynecol* 2001;185:451-458.
5. Gordis L. *Epidemiology*. 2nd ed. WB Saunders Company. P
6. Kumru S, Aydin S, Simsek M, Sahin K, Yaman M, Ay G. Comparison of serum copper, zinc, calcium, and magnesium levels in preeclamptic and healthy pregnant women. *Biol Trace Elem Res* 2003;94:105-112.
7. Ladipo OA. Nutrition in pregnancy: mineral and vitamin supplements. *Am J Clin Nutr* 2000;72:280S-290S.
8. Lazebnik N, Kuhnert BR, Kuhnert PM. Zinc, cadmium, and hypertension in parturient women. *Am J Obstet Gynecol* 1989;161:437-440.

9. Mahomed K, Williams MA, Woelk GB, Mudzamiri S, Madzime S, King IB et al. Leukocyte selenium, zinc, and copper concentrations in preeclamptic and normotensive pregnant women. *Biol Trace Elem Res* 2000;75:107- 118.
10. Norwitz ER, Robinson JN, Repke JT. Prevention of preeclampsia: is it possible? *Clin Obstet Gynecol* 1999;42:436-454.