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Competitive Interaction of Iron and Zinc in the Diet: Consequences for Human Nutrition[1]

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ABSTRACT The degree to which inhibitors of zinc bioavailability actually influence the zinc status of humans who consume usual meals and diets is not known. The interaction of iron and zinc and competitive inhibition of zinc uptake by excess iron in ratios of 2:1 or greater, when the total amount of ionic species is greater than 25 mg, appear to have a measurable effect on human zinc nutriture. The physiological basis is the competition of these chemically similar ions for some portions of a common absorptive pathway shared between inorganic (nonheme) iron and zinc; this has been demonstrated in animal experiments and in zinc absorption studies in human volunteers. Thus, studies involving formula-fed infants, experimental zinc-depletion diets and pregnant women who took prenatal vitamin-mineral supplements containing high levels of iron have shown growth delay (infants) and a decreased circulating zinc pool (all age groups), suggesting a determinant impact of excessively high Fe/Zn ratios in the diet. Consideration of solutions to these problems, including conscious adjustment of the Fe/Zn ratios in human diets, foods and therapeutic nutrient supplements in order to reduce the zinc-inhibiting effects of iron, should become a priority in policy and marketing discussions within government regulatory agencies, industry and the scientific community of human and clinical nutritionists. J. Nutr. *116*: 927–935, 1986.

INDEXING KEY WORDS iron • zinc • mineral:mineral interaction • zinc deficiency • intestinal absorption • bioavailability • pregnancy • infant formula • nutrition policy

There has been much discussion of factors that affect zinc bioavailability (1–4), but many of the inferences are based on observations with laboratory animals, poultry or livestock. It has been difficult to relate these observations to human nutrition. With respect to zinc bioavailability, the interaction of zinc with dietary iron seems to have a measurable effect on human nutrition. In the present review, I examine the physiological bases for the interaction and cite clinical and epidemiological observations that indicate a role for iron as a major determinant of zinc absorption and zinc status in humans.

ZINC-IRON INTERACTIONS IN ANIMALS

Biologically important interactions between and among chemically similar metal ions were predicted in 1970 by Hill and Matrone (5). Iron (atomic number 26, atomic weight 55.85) and zinc (atomic number 30, atomic weight 65.37) are in the first transition series of the periodic table of the elements, having identical outer electron shell configurations. Several investigators

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have reported enhanced zinc absorption in iron-depleted animals (6–10) and enhanced iron absorption with zinc depletion of rats (11). In feeding experiments with animals given diets with high Fe/Zn ratios, some laboratories found a reduction in zinc uptake (12, 13) and others did not (14–17). Hamilton et al. (9), using a murine intestinal perfusion model, showed that Fe/Zn molar ratios of 2.5:1 through 10:1 progressively lowered the efficiency of uptake of ^{65}Zn tracer from the perfusate by the intestine. A recent study in chicks, however, showed no effect of an Fe/Zn ratio of 67:1 on tissue zinc deposition (18).

INFLUENCE OF IRON ON ZINC ABSORPTION BY HUMANS

The question of the dietary interaction of iron and zinc was first addressed in metabolic balance studies of nine young women at Northwestern University by White and Gynne in 1971 (19). They fed diets providing 22 mg of iron and 11.5 mg of zinc (Fe/Zn ratio = 2). The apparent absorption of zinc in this study averaged 0.1 mg daily, an equilibrium balance, if one excludes urinary and insensible losses. The authors concluded that no competitive interaction was demonstrable from their experiment.

Since then, there have been numerous zinc absorption studies with different amounts of nonheme (inorganic) iron as the independent variable and either the acute change in circulating zinc concentration after ingestion of pharmacological amounts of zinc (the so-called zinc tolerance test) (20–24, Solomons, N.W., Pineda, O. and Milne, D. B., in preparation) or isotopic tracers (23, 25–27) as the index of zinc absorption. The results of these studies are summarized in table 1. Most of the treatments produced a competitive interaction manifested as a reduction in zinc absorption in the presence of inorganic iron.[2] The best evidence for the absorption of zinc by the mammalian intestine is that it is a *saturable* process (28, 29), implicating a carrier-mediated mechanism in the lumen-to-cell (transmucosal) transfer (30, 31). If the mechanistic speculation of a competition for receptor or carrier site (21, 23) is correct, then the data in table 1 suggest that 25 mg of *total ions* (as the sum of zinc and iron species administered as a single oral dose in solution) is the point of saturation, at which competition can begin to be expressed. Only the study of Payton et al. (25) falls outside this correlation pattern. Thus, I suggest that below this critical amount of about 25 mg of ions, given as a single dose in aqueous solution, there are sufficient sites for iron and zinc absorption without mutual interference in the adult intestinal tract.

The question of whether *heme* iron interferes with the absorption of inorganic zinc is still debated. Solomons and Jacob (20) found that a 3:1 ratio of iron to zinc, with the iron in the form of heme chloride (hemin), had no influence on zinc uptake. This is consistent with the chemical basis for the interaction (5), namely the competition between similar charged ionic species. Iron in heme is fixed in a porphyrin ring and presumably is absorbed by a pathway across the mucosal membrane different from that of the nonheme ionic iron (32). However, this demonstration (20) can be criticized because the iron in hemin, as distinct from that in intact hemoglobin or myoglobin, although heme-iron in nature, is *poorly* absorbed, and there may not have been enough transmucosal movement of the iron in the heme chloride form to produce the expected inhibition. Valberg et al. (26) used fecal monitoring of the ratio of ^{51}Cr (a nonabsorbable marker) to low-dose ^{65}Zn to study the question of heme iron interaction with inorganic zinc. They reported two-thirds lower absorption of the ^{65}Zn tracer in the presence of iron from *hemoglobin* at an Fe/Zn ratio of 5:1. However, they did not control for the effect of the protein (globin) per se. If the zinc was bound by the protein in the hemoglobin, this, rather than a competitive iron-zinc interaction, could explain the decrement in absorption efficiency. Studies with iron-free hemoglobin (or at least with a surrogate protein) in equal amounts would be needed to clarify this issue.

A curious finding in Solomons and Jacob's study (20) was that zinc from Atlantic

[2] Aggett et al. (23) also observed the reciprocal interference—that of excess zinc on the absorption of iron—in human subjects.

TABLE 1

Influence of total administered ionic species and of Fe/Zn ratio on the intestinal competition of iron and zinc in adult subjects

Zinc administered	Iron administered	Total metal ions	Fe/Zn ratio	Degree of inhibition of zinc uptake	Ref
	mg		*wt/wt*		
2.6	2.2	4.8	0.8:1	0	27
2.6	5.6	7.2	2.2:1	0	27
5.0	10.0	15.0	2:1	0	—[1]
5.0	20.0	25.0	4:1	+	—[1]
12.5	12.5	25.0	1:1[2]	+ +	22
6.0	25.0	31.0	4.2:1	0	25
12.5	25.0	37.5	2:1[2]	+ +	22
25.0	25.0	50.0	1:1	±	20
6.0	51.0	57.0	8.5:1	+ +	26
2.6	56.0	58.6	21.5:1	+ +	27
22.5	47.0	69.5	2:1	+ +	23
25.0	50.0	75.0	2:1	+ +	20, 21
25.0	60.0	85.0	2.4:1	+ +	24
25.0	75.0	100.0	3:1	+ +	20

[1]Solomons, N. W., Pineda, O. and Milne, D. B., in preparation. [2]Conducted in the presence of inorganic tin.

oysters, the most zinc-rich natural food items in the occidental diet, was impervious to the inhibitory effects of a 2:1 ratio of iron to zinc, even when 54 mg of zinc (from oysters) and 100 mg of iron as ferrous sulfate (a total of 154 mg of the metals) were given. The absence of an inhibitory interaction may be explained by the chemical form of zinc in the oyster, a physical-chemical protection against the intrusion of iron or accelerated binding of the iron or oxidation of the iron to its ferric form by the oyster flesh.

Further evidence that iron in the ferrous (divalent, reduced) oxidation state is the more potent competing species for the uptake pathway of zinc was provided by Solomons et al. (21), who found that ferric chloride was not as efficient as ferrous sulfate, at a 2:1 Fe/Zn ratio and 75 mg of total ions, in blocking the rise of zinc in the peripheral plasma; addition of the reducing agent ascorbic acid (vitamin C) to the solution of zinc and ferric salt restored the expected competition and reduced the uptake of the zinc into the plasma.

The presence of tin, as a third ionic species, failed to influence the iron-zinc interaction as determined by the zinc tolerance test (22). The competitive interaction between iron and zinc continued with the expected efficiency as if only these two competitors were present. On the other hand, Valberg et al. (26) found a synergistic (or at least additive) effect of iron and tin on the uptake of a zinc isotope in turkey meat or of $^{65}ZnCl_2$ as determined by monitoring the $^{51}Cr/^{65}Zn$ ratio in human volunteers. The possibility of enhanced impairment of zinc absorption in the presence of both tin and iron deserves further experimental consideration.

The first studies with humans in this area at Northwestern involved meals (19). Valberg et al. (26) and Sandström et al. (27) combined traces of ^{65}Zn as an isotopic tracer in meals as well. An inhibition of zinc absorption, although attenuated, was found in the turkey meat experiments of the Canadian workers (26), but the whole-body uptake of radioactivity was not reduced even by a 25:1 Fe/Zn ratio, that is, adding 56 mg of inorganic iron to the rice and meat sauce meal used by the Swedish investigators (27). These authors provided 100 mg of ascorbic acid with their meal with the hope of maintaining the iron in the ferrous form, but as the isotope was premixed into the meal, it

was probably in the ferric oxidation state and may have remained so despite the reducing agent provided with the meal. Two of three studies with *meals* fail to show an iron-zinc interaction in these single-test physiological studies. Although the interpretation is not straightforward, we must give thought to possible multiple-nutrient interactions, oxidation state changes of the iron and specific or nonspecific binding as potential confounding factors here (19, 26, 27) and in the chronic-feeding observations to be reviewed below.

IRON PRETREATMENT AND ZINC ABSORPTION

The experiments with humans cited above all used the model of *simultaneous* administration of iron and zinc in the same draught of solution or meal. Meadows et al. (33) in London examined the effect of *prior* supplementation with oral iron on the intestinal uptake of zinc. Five healthy young men and a similar number of normal young women participated in their trial. On d 1, a zinc tolerance test was performed with 50 mg of zinc alone in water. For the next 14 d the subjects took a supplement providing 100 mg of iron. They were then studied again with the simple, 50 mg zinc tolerance test. As shown in figure 1, compared with the base-line zinc response before iron treatment, the individuals had an excursion of plasma zinc that was diminished by half after the 14 d of supplementation. This finding is at variance with the experience of Solomons et al. (21), who found no reduction in zinc uptake into plasma from a 25 mg dose of zinc taken alone after iron supplementation of health volunteers, but their subjects had only been preloaded with iron, 130 mg per day, for 4 d, for a total dose of 520 mg of supplemental iron (vs. 1400 mg in the London experiment). The more intensive and prolonged treatment by Meadows et al. (33) might explain the difference in the results of the two trials.

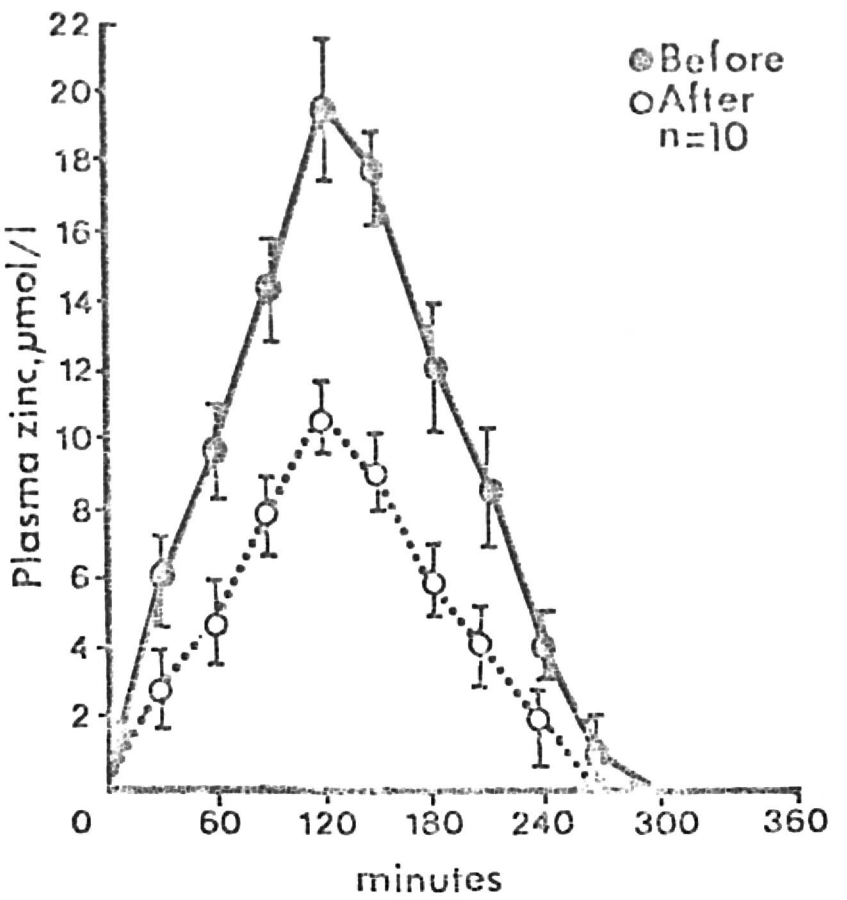

Fig. 1 Plasma concentration vs. time curve responses before and after iron and folic acid supplementation, corrected for baseline values. Points are means; bars represent the SEM. Conversion, SI to traditional units: zinc, 1 μmol/L ≈ 6.5 μg/100 ml. From Meadows et al. (33); reproduced with permission.

CLINICAL AND EPIDEMIOLOGICAL OBSERVATIONS

The bottom line for an argument supporting the existence of a truly biologically significant mineral-mineral interaction in the diet would be evidence of an impact on nutritional status itself. Perhaps the first convincing demonstration of an iron-zinc interaction came in the context of *zinc's* competition with iron: outside of Shiraz, Iran, in the rural area where the syndrome of zinc deficiency dwarfism (34) was prevalent, Mahloudji et al. (35) conducted a longitudinal supplementation study with rural schoolboys. Boys were assigned randomly to three supplemental regimens: *1*) 20 mg zinc and 20 mg iron; 2) 20 mg iron alone; 3) mineral-free placebo, given on school days 5 d/wk. Then growth was measured over a period of 20 mo. The group of children in Iran receiving both minerals together had an increase in stature equivalent to that of the group receiving mineral-free placebo over the same period. The group that was given the iron alone, however, grew an average of 5 cm more than the other two cohorts. The authors commented that "the inferior growth performance of the first group suggests interference with absorption as a result of an interaction between zinc and iron" (35).

Two other early observations can now be

interpreted, with the wisdom of hindsight, as possible examples of a nutritional impact of the iron-zinc interaction. Prasad et al. (36) conducted long-term metabolic and clinical observations on four middle-aged volunteers fed a textured soy protein-based diet, intentionally deficient in zinc. The individuals were taken in cohorts of two subjects at a time. In experiment 1 the daily zinc intake was 2.7 mg; in experiment 2 it was 3.5 mg. Curiously, in the former cohort a daily iron intake of 130 mg (Fe/Zn ratio of 50:1) was provided, but this was reduced to 20.3 mg (Fe/Zn ratio of 6:1) in the second group of subjects. At the same time, although there was only a 25% lower daily intake of zinc in the first experiment, there was a proportionally much greater initial degree of negative zinc balance in the subjects of that experiment; moreover, whereas the plasma zinc levels remained virtually stable for 9 mo in experiment 2, the levels in experiment 1 fell by 25 and 30% during the first 3 mo of the study.

Walravens and Hambidge (37) followed a cohort of white infants from middle-class families in Denver for the first 6 mo of life. One group received a conventional formula of that era (Similac plus iron), containing 1.8 mg of zinc per liter of prepared diet; the other group received a zinc-supplemented formula with 5.8 mg of zinc per liter. The groups were randomly assigned, and the treatment was blind to mothers and investigators alike. After 6 mo the male infants on the zinc-supplemented diet had grown 2.1 cm more ($P < 0.025$) than the infants fed the conventional formula, and had gained 535 g more weight ($P < 0.05$). Also, for males the mean plasma zinc levels at 6 mo were 80.5 ± 3.7 and 69.5 ± 3.2 μg/dl in the respective dietary groups ($P < 0.025$). This was unexpected, as no reason for marginal zinc nutriture in healthy infants fed a conventional commercial baby formula would have been anticipated. The formula, however, was *iron-enriched*, with at least 12 mg of iron per liter. Thus, the Fe/Zn ratios were 2:1 in the zinc-supplemented formula and 6:1 in the standard formula. Solomons and Jacob (20) suggested that the additional iron was a factor in the impaired growth of the unsupplemented infants.

Recently, Craig et al. (38, 39) looked at the issue of Fe/Zn ratios *prospectively* in 12- to 16-wk-old infants in a cross-sectional survey. Two milk-based formulas—Similac and Enfamil—were compared. All milk formulas had more than 6 mg of zinc per liter, but the iron-fortified products obviously had greater Fe/Zn ratios. The intakes and Fe/Zn ratios are shown in table 2. The plasma zinc concentration for children fed the unfortified cow milk formula was 77.5 ± 13.4 μg/dl (± SD); with the fortified cow milk formula it was 61.6 ± 12.9 μg/dl; and with high-iron *soy* formula it was 45.1 ± 19.1 μg/dl. The plasma zinc levels as a function of the iron content of cow milk-based diets were significantly different ($P < 0.05$). Soy formula also had a lower zinc concentration. Some of the response could be due to the factors in soy protein itself (3), but a component of the reduced plasma circulation of zinc could also be related to its iron content.

TABLE 2

Iron, zinc and copper levels of infant formulas[1]

Formula	Iron	Zinc	Copper	Fe/Zn
		mg/L		
Cow milk based				
Similac	2.40 ± 0.13[2]	6.50 ± 0.06	1.06 ± 0.10	0.37
Enfamil	1.44 ± 0.01	6.54 ± 0.05	0.80 ± 0.05	0.22
Cow milk based, iron fortified				
Similac with iron	14.94 ± 0.02	6.77 ± 0.03	0.88 ± 0.18	2.2
Enfamil with iron	13.90 ± 0.49	6.23 ± 0.27	0.80 ± 0.01	2.2
Soy based				
Isomil	19.44 ± 0.33	6.18 ± 0.04	1.30 ± 0.12	3.1
Prosobee	13.94 ± 0.06	6.30 ± 0.01	1.09 ± 0.07	2.2

[1]From Craig et al. (38); reproduced with permission. [2]Mean ± SD; n = 2 or 3.

One of the conditions for which the greatest daily iron intake is recommended by physicians and dieticians is pregnancy. Several recent studies of pregnant women who took iron in their prenatal vitamin-mineral supplements have suggested an effect on zinc status related to the level of iron intake. Hambidge et al. (40) studied 46 women in Denver, Colorado, with serial determinations of plasma zinc and other nutritional indicators. They also estimated zinc and iron intakes from food and prenatal supplements. As shown in figure 2, there was an inverse association between the level of iron in prenatal supplements and the zinc level. This held true for all three trimesters. The activity of alkaline phosphatase, a zinc metalloenzyme, was also inversely related to the intake of supplemental iron. Campbell-Brown et al. (41) in Britain studied 91 Asian and 51 European women during pregnancy. In the three women who reported taking more than 100 mg of iron daily as a supplement in the weeks prior to blood sampling, the mean zinc level was 46 μg/dl—well below the 56 μg/dl average for the group as a whole. Breskin et al. (42) studied 37 diabetic women and 69 control women in Seattle throughout pregnancy and measured serum zinc concentrations at intervals. They found that any type of supplement with or without zinc, but containing at least 30–60 mg of iron, was associated with significantly lower zinc levels than when smaller amounts of iron were present. However, in the experience of Sheldon et al. (43) with 25 British women, 15 without iron supplementation and 10 receiving 480 mg of ferrous fumarate daily (160 mg of elemental iron), followed from early pregnancy to 12 wk postpartum, there were no differences between serum zinc concentrations in the two groups at any interval. Thus, the first three studies cited (40–42), but not the last (43), suggest that high intakes of iron by pregnant women as part of their prenatal supplementation regimen reduce the circulating zinc levels.

Finally, Mukherjee et al. (44) studied 439 pregnant women in Dayton, Ohio, throughout gestation. They observed, paradoxically, a *positive* correlation between plasma iron

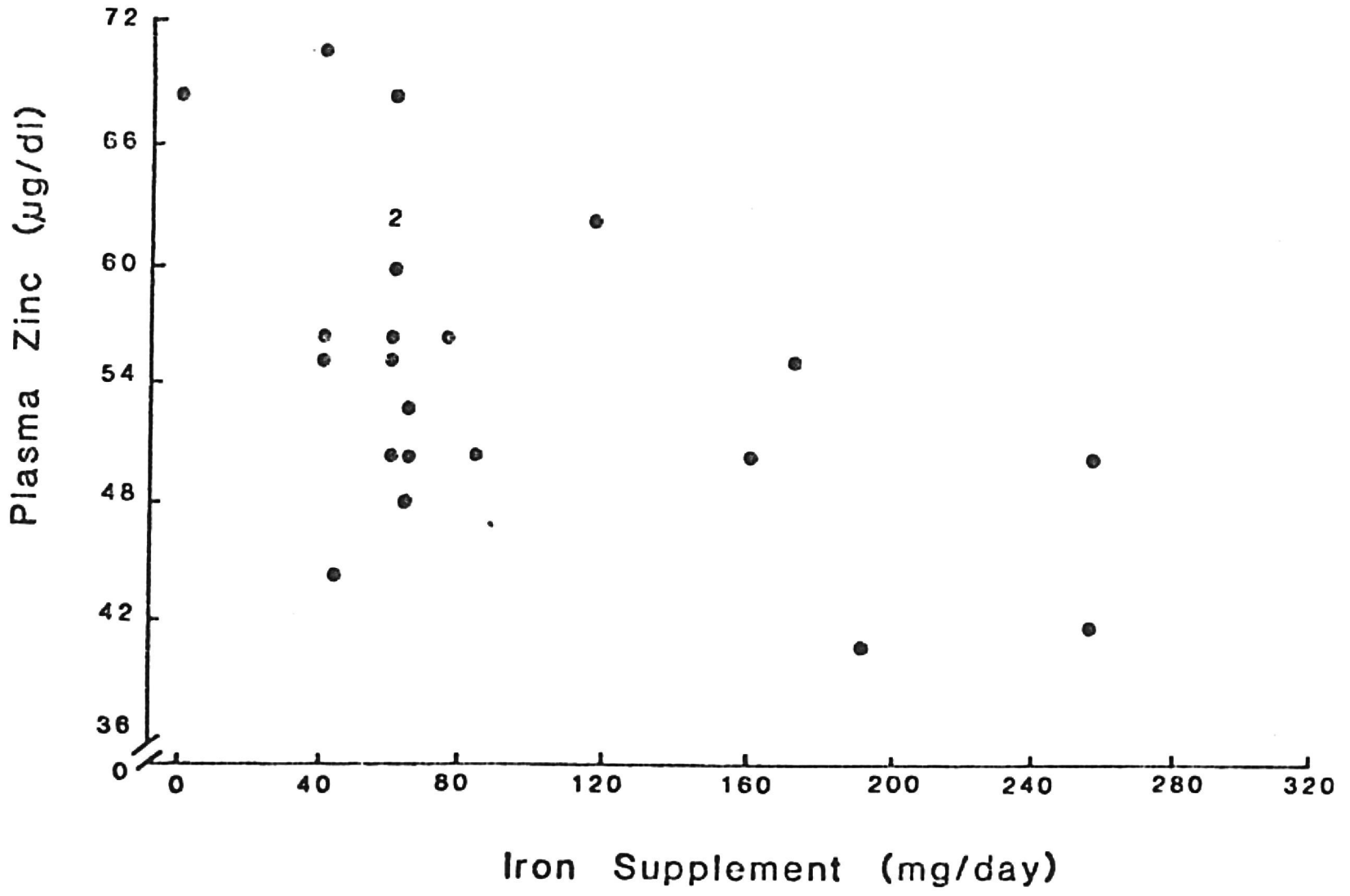

Fig. 2 Plasma zinc vs. level of prenatal iron supplementation at 9 mo of gestation. From Hambidge et al. (40); reproduced with permission.

and plasma zinc in all trimesters (r values ranging from 0.39 to 0.48, $P < 0.0001$). Iron was measured in this study by direct aspiration of the diluted plasma into an atomic absorption spectrophotometer, without prior protein precipitation. Thus, a contribution to measured iron from microhemolysis might have obscured the true relation between the plasma zinc and iron variables in this report (45,46).

SUMMARY STATEMENT

In summary, although definitive prospective studies, well-designed and using random assignment and multiple dosage levels of zinc and iron taken in the context of a usual mixed diet, have not yet been conducted, the consensus of evidence at hand suggests strongly that excessive intakes of iron as supplements or in formulated foods can impair indices of zinc status such as growth in infants and circulating zinc levels in all age groups (36–42). Although plasma or serum zinc is certainly not an unequivocal arbiter of total-body zinc nutriture (47), many of the studies cited involved *serial* measurements of these indices, adding reliability to the meaning of any changes in this variable in terms of a change in the actual zinc status of the subjects.

The risks for optimal nutrition posed by iron deficiency—with or without overt anemia—are considerable, but the effort to ensure iron-repleted conditions for members of the populations with a greater propensity to develop iron depletion, such as infants and pregnant or lactating women, must be tempered by a concern for adverse effects on *zinc* status. Two avenues are open. One is to reduce the levels of iron added to baby foods, formulas and prenatal vitamin-mineral supplements. The other is to adjust the iron/zinc ratios in the total dietary package of nutrients. Although when zinc and iron are taken with meals, a damping of their interaction is observed in absorption experiments, the epidemiological observations with infant foods suggest that it is still significant in a dietary context. If one can justify the need for a high, chronic level of iron, then *supplementation* (ratio balancing) with zinc would seem a logical solution.

Converging findings from laboratory animal studies, physiological experiments with human volunteers and clinical and epidemiological observations of men and women lead to the irresistible conclusion that a finite risk of impaired zinc nutriture in humans is attendant on excessive intake of, at least, inorganic iron in the diet or as a supplement. Appropriate solutions are needed to ensure that a well-intentioned practice such as enriching diets with iron to prevent deficiency and anemia does not have adverse consequences in a reciprocal sense, i.e., promoting marginal deficiency states with respect to zinc. This is especially important for infants and pregnant women, given the role of zinc in growth (37, 48) and in fetal health and pregnancy outcome (32, 49, 50).

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