Volume-9,Issue-5(May-18)
ISSN (O) :- 2349-3585

A SYSTEMATIC REVIEW ON ASF SUPPLEMENTS TO IMPROVE THE IRON STATUS OF RURAL REPRODUCTIVE - AGE WOMEN

Ammara Zakir[1], Zaeem Zafar[2], Mariyam Rashid[3],Nida Qamar[4]
[1]Amna Inayat Medical College, Sheikhupura, Pakistan,[2]University College of Medicine & Dentistry, Lahore, Pakistan, [3]Nishtar Medical University, Multan, Pakistan, [4]University of Health Sciences, Lahore, Pakistan

Abstract:Every day ASF supplements enhanced normal micronutrient intake and the iron status of rustic reproductive-age women. This methodology could be adjusted to a larger-scale mediation to convey normal intake of at-risk micronutrients to RDA levels for pregnancy utilizing satisfactory nearby nourishment sources. Because of national agriculture help to advance family generation of these sustenances, this methodology may likewise give a possible other option to supplementation in remote provincial territories. The watched defensive impact of iron status against UTI and the expansion in UTI occurrence due to iron-rich ASF supplementation are already unreported marvels and require further research.

Keywords: systematic review, iron status, rural reproductive-age women

I. Introduction

Undernutrition, the Life Cycle, and Pregnancy

Nutrition throughout the human life cycle can be thought of as a series of interrelated stages, where the quality of one will in large part determine the quality of the next (20). The nutritional adequacy a mother provides her developing fetus in utero determines the nutrient stores of the infant at birth and influences the infant's resistance to infection. Infants who were undernourished in utero are more susceptible to infection (21), and frequent infections in turn further reduce their ability to absorb and utilize nutrients (22, 23). Without supplementation or use of nutrient-rich complementary foods, these infants remain undernourished throughout lactation and become undernourished toddlers and then undernourished children, who are chronically more susceptible to infection and unable to fulfill their nutrient needs for growth and immunity. Stunting results and those who survive will likely become small, undernourished adolescents and adults – including the next generation of reproductive-age women. When these women become pregnant, their diets and body nutrient stores fall short of nutrient demands for fetal development and maternal immunity, they gain little weight during pregnancy, are more likely to suffer from pregnancy complications, and they give birth to small, undernourished infants. Though the role of the life cycle in undernutrition is well-known, comparatively little emphasis has previously been placed on understanding the potentially profound interactive nature of undernutrition and immunity at what may be the most critical stage of this cycle: pregnancy.

II. Systematic review

ASF and diet quality

In any given population, it is unlikely that the disparity in positive pregnancy outcomes observed among marginally-nourished women compared to those with higher quality diets can be attributed to deficiency of a single micronutrient (24). Optimal nutrition during pregnancy is determined both by the nutrient demands for fetal growth and development and by the nutrient demands for optimal maternal health. Inflammation and infection during pregnancy can have severe consequences for the mother and fetus, and several micronutrient deficiencies may contribute to the likelihood of infections and resulting maternal complications. Furthermore, single micronutrient deficiencies rarely occur in isolation, and several micronutrients are important for immune and developmental processes during pregnancy. ASF is a high quality source of protein, and it provides an amino acid balance well-suited to human function. ASF is also an excellent source iron, zinc, riboflavin, and it is only source of preformed vitamin A and of vitamin B12.

Phytate, or myo-inositol hexaphosphate, is a molecule present in plant source foods, particularly whole grains, the skins of beans, seeds, and leafy vegetables. Phytate serves as a form of stored energy for cellular metabolism in plants, and its mineral-chelating effect allows plants to sequester iron and zinc and prevent these nutrients from being used by invading bacteria. Consequently, plant source foods high in iron and zinc are generally also high in phytate, and the iron and zinc from these foods is less bioavailable. Absorption of heme-iron from ASF is not inhibited by phytate, and is estimated to be about 20% to 40% (25), while absorption of inorganic iron from high-phytate cereal-based meals is as low as 2% to 3% (26). Since phytate also inhibits zinc absorption, the absorbable fraction of zinc in a meal can be estimated by the phytate to zinc molar ratio (27). The presence of ASF also enhances the absorption of inorganic iron (25) and zinc (28) from mixed meals, and reduces the inhibitory effects of phytate on zinc. Therefore, consumption of relatively small amounts of ASF can contribute substantially to overall dietary quality in terms of iron and zinc bioavailability. The following sections are a brief review of micronutrient deficiencies implicated in abnormal fetal development, pregnancy complications, and poor birth outcomes; the roles of these micronutrients in immune function.

Iron

The majority of iron in the body is part of hemoglobin, which takes advantage of the redox potential of iron to deliver oxygen from the lungs to tissues. The transition between ferrous and ferric oxidative states is also necessary for cellular respiration, DNA synthesis, and generation of reactive oxygen species utilized in immune defense. Iron is stored in the liver and bone marrow, primarily inside ferritin, and these stores can be mobilized to support hemoglobin production. Reproductive-age and pregnant women have higher iron requirements due to current and prior menstrual blood loss and demands for fetal growth, and often do not have enough iron in their diets to meet these needs, especially where diets are high in phytate and contain little heme iron (26). In regions where hookworm infections are endemic, and increase iron losses, the risk of deficiency is further increased (29). When iron stores are depleted due to inadequate intake and/or excessive losses, iron is no longer available for hemoglobin production and erythropoiesis, and iron deficiency anemia results, characterized by abnormally small, hypochromic erythrocytes. During pregnancy, iron demand increases to meet the needs for fetal growth and build- up of fetal iron stores in the third trimester of pregnancy (30), and pregnant women are more likely to exhibit signs of anemia in the latter stages of pregnancy. Body iron stores before pregnancy predict maternal iron status during pregnancy and risk of anemia (31, 32). Despite increased iron absorption during pregnancy, it is difficult to replenish depleted maternal iron stores with supplementation during pregnancy (33). Maternal iron status can also predict infant iron stores (34). Infants of iron supplemented mothers in Niger exhibited higher iron status three months after birth (35). In rhesus monkeys, iron status before conception predicted infant iron status at birth, independent of whether the mother received a richly iron-fortified diet throughout pregnancy (36). Since depleted iron stores are not easily replenished after pregnancy begins, programs to improve iron status in reproductive-age women are likely to be more successful when initiated prior to pregnancy (31). Observational studies have implicated iron deficiency during pregnancy in risk of low birth weight, preterm delivery, and maternal mortality (30). The effectiveness of iron supplementation in reducing these outcomes is somewhat equivocal, possibly due to poor study design (37), late timing of supplementation with respect to gestation, or due to interactions with other micronutrient deficiencies undetected in these populations. Mechanisms by which iron deficiency may play a role in these outcomes include the effect of iron deficiency on stress hormones which regulate gestational duration, the chronic hypoxia of anemia which can induce stress hormone responses, and oxidative stress and subsequent fetal-placental oxidative damage (38). However, iron excess due to over-supplementation may promote similar oxidative stress (39, 40). Iron has several important roles in immune function. Iron is necessary for the activity of myeloperoxidase used by macrophages, neutrophils, and natural killer (NK) cells in the formation of

ISSN:-2349-3585 |www.ijrdt.org

toxic hydroxyl radicals. Although macrophages are capable of acquiring iron during iron deficiency by engulfing and phagocytosing erythrocytes, neutrophils and NK cells are dependent upon surface transferrin receptor for iron delivery, and exhibit reduced myeloperoxidase activity and reduced migration to inflammatory sites during iron deficiency (41). Therefore, neutrophil and NK cell-mediated capacity of the immune system to kill intracellular pathogens is likely impaired with inadequate iron. Iron can also influence the differentiation of naïve T-cells to helper-T (TH) cells. When iron is not available, naïve T-cells fail to differentiate. However, the differentiation of pro- inflammatory TH1 cells is more susceptible to inadequate iron than that of TH2 cells. Therefore, marginal iron status may cause a shift from TH1 to TH2 mediated immunity, reducing the capacity to the immune system to provide memory response to extracellular pathogens (42). However, the prevalence of anemia among reproductive age women in many rural areas remained high. In 2001, 54% of non-pregnant women between 15 and 49 years old living in DakLak Province of the central highlands were anemic (44). In a 2006 survey conducted in Yen Bai Province (about 150 km northwest of Hanoi), 37.5% of the non-pregnant women between 16 and 45 years old were anemic. Although 78% had hookworm eggs in stool, frequency of intake of animal source foods (ASF), including meat, poultry, fish, and eggs, was more strongly correlated with hemoglobin status than were hookworm egg counts (45). In these studies, the proportion of anemia due to iron deficiency was not determined. Anemia and helminthic infections were present among children as well. In the Tam Nong District of PhuTho (about 80 km northwest of Hanoi), 25% of primary school children were anemic; however, only 2% of these children had iron deficiency (transferrin receptor > 8.5 µg/mL), suggesting that iron deficiency played little or no role in the high prevalence of anemia (46). In the same study, helminthic infections were exceedingly common; 92% tested positive for intestinal helminthes: 76% for trichuris, 6% for hookworm, both are risk factors for anemia, and 71% tested positive for ascaris. Among these children, infection with trichuris and hookworm was negatively correlated with hemoglobin concentrations, and those with both trichuris and hookworm were the most likely to be anemic. Although the type of infection is related to risk for anemia among these children, these data do not eliminate nutrition from the potential causal pathway. It is possible that chronic undernutrition of multiple micronutrients made these children more susceptible to infections which in turn increased their risk for anemia. Their relatively good iron status could be explained by the existence of iron supplementation programs for school-age children. Furthermore, anemia has multiple potential causes not limited to iron deficiency and infections. Some of these other causes that may be relevant to rural areas include blood loss (particularly for reproductive-age women using intrauterine contraceptive devices), thalassemia, and vitamin B12 deficiency.

Zinc

Zinc has more diverse metabolic and structural functions than any other single micronutrient, and serves as a component or cofactor of more than 200 enzymes. Zinc is necessary for DNA transcription and repair, insulin storage and release, oxidative defense, membrane integrity, and immune function. Dietary absorption of zinc is a regulated and saturable process, mediated primarily by the zinc import protein Zip4 at the apical membrane and zinc export protein ZnT1 at the basolateral membrane of epithelial cells lining the lumen of the small intestine (47). Fractional zinc absorption increases in late pregnancy in women with marginal zinc intakes (48) and in women with normal zinc intakes (49). Though most cells appear to hold small reserves of zinc for cellular function, there are no major body stores for zinc, and status is primarily determined by current zinc intake and plasma zinc levels (50). Absorption of zinc from meals is enhanced by the presence of animal protein, and inhibited by the presence of phytate (51).

Zinc deficiency during pregnancy has been implicated in low birth weight, preterm delivery, and maternal complications including pregnancy-induced hypertension, hemorrhage, and infection (52). Animal data suggest that severe gestational zinc deficiency can lead to depressed immune function in the offspring for multiple generations (53). Although severe zinc deficiency is rare, there is growing evidence that mild and moderate zinc deficiencies, which are common in many

ISSN:-2349-3585 |www.ijrdt.org

populations but difficult to detect in individuals, have significant metabolic and immunological consequences (27, 54, 55) and may therefore contribute to poor pregnancy outcomes. For example, in mild and moderate zinc deficiency, zinc-dependent oxidative defense mechanisms and immune function may be impaired. Zinc is necessary for the activity of copper- zinc superoxide dismutase (SOD), which converts the superoxide anion to hydrogen peroxide. By removing superoxide radicals, SOD prevents oxidative damage within cells and in blood. The hydrogen peroxide product of SOD is also important for innate immunity. Upon ingestion of microorganisms, macrophages express SOD and produce large amounts of hydrogen peroxide, which can be used to kill bacteria directly, or further converted to bactericidal hypochlorite and hydroxyl radicals by myeloperoxidase using a ferrous ion as cofactor (56, 57). Zinc also contributes to the defense against lipid peroxidation and membrane damage by reactive oxygen species (ROS) produced in this process (58).

In mice fed a zinc deficient diet for 30 days, macrophages exhibited a reduced ability to destroy a pathogenic parasite, Trypanosomacruzi, once internalized. Treatment of these macrophages with a solution containing zinc restored their ability to destroy the internalized parasite similar to that of macrophages from mice fed a zinc-adequate diet (59). More recently, rats infected intraperitoneally with the same parasite recovered more quickly when supplemented with zinc, and macrophages at the site of infection had higher concentrations of ROS (60). Zinc is a cofactor of thymulin, a peptide hormone that stimulates cytokine release and T- cell differentiation. Zinc deficiency has been shown to decrease thymulin activity in humans, and reduces the size of the thymic cortex. Zinc deficiency can also create an imbalance in TH1 and TH2 mediated immune function. In healthy adult males, a moderately zinc deficient diet (5 mg/d) resulted in reduced expression of the TH1 cytokines interferon-gamma and interleukin (IL)-2, while TH2-related cytokines remained unaffected (61). Acquired immune response to extracellular pathogens may therefore be reduced under conditions of zinc deficiency. These specific alterations in immune function during zinc deficiency may therefore interfere with normal coordinated immune responses and contribute to increased susceptibility to infectious disease or altered immune function during pregnancy. Little is known about the zinc status of reproductive-age women in rural areas. Due to the growth-limiting nature of zinc deficiency, a stunting rate of > 20% has been proposed as a cutoff for determining whether substantial risk for zinc deficiency exists in a population, and therefore further assessment of zinc status should be considered (27). The most recently published national data has the rate of stunting among children under 5 year old at about 30% in 2000 and in 2005 (12). In a 2013 sample of children between 1 to 5 years old in rural Thai Nguyen, 87% were zinc deficient (65). One small study published by the NIN in 2006 reported 37.5% anemia and serum zinc concentrations of 111.7 ± 47.5 µg/dL (mean ± SD) among 72 females between 20 and 60 years old living in rural Ba Vi (66). This is unusually high, suggesting that samples were hemolyzed or contaminated. An estimated 18% were zinc deficient, assuming normally- distributed data and a 70 µg/dLcutoff for deficiency (27), but this was not presented in the paper. Further, trace-element grade tubes were not used for sample collection (personal communication), and could have led to underestimation of the true prevalence of zinc deficiency in this sample. Approximately 55% (31/59) of lactating mothers participating in a 2015 study in rural BacGiang Province had serum zinc below 70 µg/dL, with a median (95% confidence interval) of 68 (60, 79) µg/dL, and 39% were anemic. In this study, although trace-element grade tubes and sample processing techniques were used, the blood was allowed to clot for up to 3 h at ambient May temperatures before spinning to collect sera (67). The length of incubation at likely high ambient temperature could have caused zinc to leach out of cellular components of the blood samples (68), and serum zinc values were therefore probably artificially high. In 2009, we conducted a survey of non-pregnant reproductive-age women in the Cam Khe District of PhuTho Province (about 50 km northwest of the Ba Vi site) and 81% had low plasma zinc (data presented in Chapter 3).

Vitamin A

Vitamin A refers to retinoids that have the biological activity

ISSN:-2349-3585 |www.ijrdt.org

of all-trans retinol, retinal, or retinoic acid. Due to its role in gene regulation mediated by retinoic acid receptors (RAR), vitamin A has important roles in embryonic development, membrane integrity, cell differentiation, and immune function. Vitamin A is stored in the liver as retinyl esters. As liver stores are diminished, immune response to infection is impaired. When stores are nearly depleted, night blindness develops. If untreated, ocular lesions can follow, eventually leading to xerophthalmia and irreversible blindness. In Nepal, women with night blindness are five times more likely to die of pregnancy- related complications than women without night blindness (69). Provision of vitamin A supplements to night blind Nepali women reduced childbirth-related mortality by nearly 50%, reduced the duration of labor, and reduced the duration of reported illness in the last trimester of gestation (70). Vitamin A supplementation has also been associated with increased effectiveness of iron supplements and reduced risk of maternal anemia (71), possibly due to the role of retinoic acid in modulating the RNA-binding activity of iron regulatory proteins (72). Vitamin A metabolism may also depend on zinc. In a study of pregnant Indonesian women who appeared to have adequate zinc status, those who were supplemented with zinc and β-carotene had higher serum retinol six months postpartum than those who were supplemented with β- carotene alone (73). Though the mechanism behind this effect of zinc on utilization of β-carotene is not known, it has been proposed that 15-15'-dioxygenase, which splits β-carotene centrally to retinol, may depend on zinc (73). Zinc-dependent enzymes involved in retinyl ester hydrolysis and synthesis may also play a role in the apparent interaction between zinc and vitamin A (74).

Although vitamin A supplementation can be effective in reducing the risk of death due to infection in deficient populations, the specific mechanisms by which vitamin A can mediate immune function are complex and not well-understood. Vitamin A deficiency leads to loss of mucous-producing goblet cells and to compromised mucosal epithelial barriers of the eye, gastrointestinal tract, and urogenital tracts (75). The resulting squamous metaplasia makes the epithelium more vulnerable to penetration by pathogens. Vitamin A supplementation has been associated with improved recovery from diarrheal disease (23), and in Gambian children recovering from diarrhea, those receiving vitamin A supplements had more rapid regeneration of gut mucosal barriers (76). Retinoic acid is needed for activity of neutrophils, macrophages, and NK-cells. Vitamin A deficiency can decrease neutrophil migration and phagocytosis while increasing neutrophil count (77), and in rats, lead to lower removal of bacteria from the blood stream (78). Since retinoic acid is also necessary for suppression of pro-inflammatory IL-12 production by macrophages, vitamin A deficiency may indirectly lead to excessive self-stimulation of macrophages and increased oxidative stress due to the spontaneous release of ROS (75). Evidence from humans supports the role of vitamin A deficiency in altering pro-inflammatory and anti-inflammatory cytokine profiles, in increasing macrophage proliferation and inflammation (79), and in reducing macrophage phagocytic capacity in vitro (80). NK-cell proliferation on the other hand is decreased by marginal vitamin A status in rats (81), and vitamin A deficiency decreases NK-cell number and their ability to kill virus-infected cells (82). Vitamin A also plays important roles in acquired immunity by impairing TH2-mediated antibody responses. For example, response to tetanus toxoid vaccine in children with marginal vitamin A status (83) and, in infants, to diphtheria vaccine (84) and oral polio vaccine (85) are increased by vitamin A supplementation. Recent in vitro studies of the role of retinoic acid in T-cell differentiation may provide further mechanistic insight into how vitamin A might suppress inflammation. Transforming growth factor (TGF)-β suppresses naïve T cell differentiation into TH1 and TH2 cells. However, in combination with pro-inflammatory IL-6, TGF-β stimulates T-cell differentiation to pro- inflammatory TH17 cells. Retinoic acid derived from dendritic cells is the primary regulator of this process, and is capable of both inhibiting TH17 differentiation and promoting anti-inflammatory regulatory T (Treg) cell differentiation (86). In addition, dendritic cells from mice fed a diet deficient in vitamin A, when isolated and exogenously treated with

ISSN:-2349-3585 |www.ijrdt.org

retinoic acid, and then reintroduced into the mouse circulation, stimulated IL-4 dependent TH2 differentiation necessary for antibody production pathways (87). Therefore, the vitamin A status of dendritic cells can determine the balance of pro-inflammatory and anti-inflammatory immune profiles. Abnormal TH1/TH2 ratios in pregnancy have been implicated in risk of spontaneous abortion, intrauterine growth restriction, preeclampsia, and preterm delivery (88). In rural areas, subclinical vitamin A deficiency remains a problem for reproductive-age women. A survey conducted in 2000 reported that 43% of lactating mothers had low concentrations of vitamin A in their milk (94). Although the main source of vitamin A among these women was from plant sources, the conversion of carotenoids to retinol, a function influenced by zinc (73), was less efficient than expected (95). The zinc status of these women is not known, and the likelihood of widespread zinc deficiency in rural areas suggests that their zinc status could have a role in the efficiency of β-carotene conversion to active vitamin A.

Vitamin B12 and Folate

Folate, a term for molecules with the biological activity of folic acid, and vitamin B12 are both essential for generation of one-carbon units used in regeneration of methionine from homocysteine and in DNA synthesis and repair. Deficiencies of either nutrient can lead to elevated plasma homocysteine levels, increased rates of misincorporation of deoxyuridylate (dUMP) in place of deoxythymidilate (dTMP) during DNA synthesis and repair, and to the inability of red blood cells to fully mature, leading to megaloblasticanemia. Elevated plasma homocysteine levels have been related to risk of pregnancy complications including recurrent spontaneous abortion, intrauterine death, placental abruption, neural tube defects and low birth weight (96-99). Marginal status of either vitamin B12 or folate is in turn related to elevated homocysteine and the risk of similar pregnancy complications. Independent of folate, low maternal serum vitamin B12 concentrations have been associated with intrauterine growth restriction (100) and neural tube defects (101). Very little data exist which characterize folate or vitamin B12 intakes or status of rural areas women or children. Although gathered vegetables make a significant contribution to the folate intakes of rural women (102), the only food sources of vitamin B12 are ASF. Due to low intakes of ASF, low vitamin B12 intake may be common among reproductive-age women in rural areas (data presented in Chapter 3). Vitamin B12 status may also be affected due to decreased absorption by infection with Helicobacter pylori (103). No surveys have been conducted among reproductive-age women in rural areas. However, 53% were below the cutoff of 905 nmol/L RBC for folate associated with lower risk of neural tube defects (106).

III. Research gap

Multiple micronutrient deficiencies appear to be present among large proportions of women and children in rural areas, and likely affect diverse and complex physiological functions. At a minimum, these deficiencies can alter the function of immune cells, possibly increasing susceptibility to infections, which in turn cause further nutrient losses, and altering the balance of pro- and anti-inflammatory cytokines needed for placental development and maintenance of healthy pregnancy. As these deficiencies are prolonged, fetal transfer of nutrients, fetal and infant growth are likely to be reduced, as evidenced by high rates of low birth weight and stunting among rural children.

References

1. Giay T. Utilisation of wartime nutrition survival experiences. Asia Pac J ClinNutr 1998;7:311-13.

2. FAOSTAT Food Balance Sheets. Food and Agriculture Organization of the United Nations, 2009.

3. United Nations. Administrative Committee on Co-ordination. Sub-committee on Nutrition., International Food Policy Research Institute. 4th report on the world nutrition situation : nutrition throughout the life cycle. Geneva: United Nations Administrative Committee on Coordination Subcommittee on Nutrition, 2000.

4. Moore SE, Collinson AC, TambaN'Gom P, Aspinall R, Prentice AM. Early immunological development and mortality from infectious disease in later life.ProcNutrSoc 2006;65:311-8.

5. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. Geneva,: World Health Organization,

1968.

6. Brown KH. Diarrhea and malnutrition. J Nutr 2003;133:328S-332S.

7. Keen CL, Clegg MS, Hanna LA, et al. The plausibility of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications. J Nutr 2003;133:1597S-1605S.

8. Hallberg L, Hulthen L. Prediction of dietary iron absorption: an algorithm for calculating absorption and bioavailability of dietary iron. Am J ClinNutr 2000;71:1147-60.

9. Hurrell RF. Influence of vegetable protein sources on trace element and mineral bioavailability. J Nutr 2003;133:2973S-7S.

10. Brown KH, Rivera JA, Bhutta Z, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull 2004;25:S99-203.

11. Sandstrom B, Cederblad A. Zinc absorption from composite meals. II. Influence of the main protein source. Am J ClinNutr 1980;33:1778-83.

12. Crompton DW, Nesheim MC. Nutritional impact of intestinal helminthiasis during the human life cycle. Annu Rev Nutr 2002;22:35-59.

13. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. Am J ClinNutr 2005;81:1218S-1222S.

14. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J ClinNutr 2000;72:257S-264S.

15. Casanueva E, Pfeffer F, Drijanski A, Fernandez-Gaxiola AC, Gutierrez-Valenzuela V, Rothenberg SJ. Iron and folate status before pregnancy and anemia during pregnancy. Ann NutrMetab 2003;47:60-3.

16. Milman N, Bergholt T, Byg KE, Eriksen L, Graudal N. Iron status and iron balance during pregnancy. A critical reappraisal of iron supplementation.ActaObstetGynecolScand 1999;78:749-57.

17. Allen LH. Multiple micronutrients in pregnancy and lactation: an overview. Am J ClinNutr 2005;81:1206S-1212S.

18. Preziosi P, Prual A, Galan P, Daouda H, Boureima H, Hercberg S. Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. Am J ClinNutr 1997;66:1178-82.

19. Lubach GR, Coe CL. Preconception maternal iron status is a risk factor for iron deficiency in infant rhesus monkeys (Macacamulatta). J Nutr 2006;136:2345-9.

20. Rasmussen K. Is There a Causal Relationship between Iron Deficiency or Iron-Deficiency Anemia and Weight at Birth, Length of Gestation and Perinatal Mortality? J Nutr 2001;131:590S-601S; discussion 601S-603S.

21. Allen LH. Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. J Nutr 2001;131:581S-589S.

22. Anetor JI, Ajose OA, Adeleke FN, Olaniyan-Taylor GO, Fasola FA. Depressed antioxidant status in pregnant women on iron supplements: pathologic and clinical correlates. Biol Trace Elem Res 2009.

23. Lachili B, Hininger I, Faure H, et al. Increased lipid peroxidation in pregnant women after iron and vitamin C supplementation. Biol Trace Elem Res 2001;83:103-10.

24. Brock JH, Mulero V. Cellular and molecular aspects of iron and immune function. ProcNutrSoc 2000;59:537-40.

25. Thorson JA, Smith KM, Gomez F, Naumann PW, Kemp JD. Role of iron in T cell activation: TH1 clones differ from TH2 clones in their sensitivity to inhibition of DNA synthesis caused by IgGMabs against the transferrin receptor and the iron chelatordeferoxamine. Cell Immunol 1991;134:126-37.

26. Liuzzi JP, Cousins RJ. Mammalian zinc transporters.Annu Rev Nutr 2004;24:151-72.

27. Donangelo CM, Zapata CL, Woodhouse LR, Shames DM, Mukherjea R, King JC. Zinc absorption and kinetics during pregnancy and lactation in Brazilian women. Am J ClinNutr 2005;82:118-24.

28. Harvey LJ, Dainty JR, Hollands WJ, et al. Effect of high-dose iron supplements on fractional zinc absorption and status in pregnant women. Am J ClinNutr 2007;85:131-6.

29. Chung CS, Stookey J, Dare D, et al. Current dietary zinc intake has a greater effect on fractional zinc absorption than does longer term zinc consumption in healthy adult men. Am J ClinNutr 2008;87:1224-9.

30. Lonnerdal B. Dietary factors influencing zinc absorption. J

Nutr 2000;130:1378S-83S.

31. King JC. Determinants of maternal zinc status during pregnancy. Am J ClinNutr 2000;71:1334S-43S.

32. Beach RS, Gershwin ME, Hurley LS. Gestational zinc deprivation in mice: persistence of immunodeficiency for three generations. Science 1982;218:469-71.

33. Hall AG, Kelleher SL, Lonnerdal B, Philipps AF. A graded model of dietary zinc deficiency: effects on growth, insulin-like growth factor-I, and the glucose/insulin axis in weanling rats. J PediatrGastroenterolNutr 2005;41:72-80.

34. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J ClinNutr 1998;68:447S-463S.

35. Aderem A, Underhill DM. Mechanisms of phagocytosis in macrophages. Annu Rev Immunol 1999;17:593-623.

36. Bogdan C, Rollinghoff M, Diefenbach A. Reactive oxygen and reactive nitrogen intermediates in innate and specific immunity. CurrOpinImmunol 2000;12:64-76.

37. Powell SR. The antioxidant properties of zinc. J Nutr 2000;130:1447S-54S.

38. Wirth JJ, Fraker PJ, Kierszenbaum F. Zinc requirement for macrophage function: effect of zinc deficiency on uptake and killing of a protozoan parasite. Immunology 1989;68:114- 9.

39. Brazao V, Filipin MD, Caetano LC, Toldo MP, Caetano LN, Prado JC, Jr. Trypanosomacruzi: The effects of zinc supplementation during experimental infection. ExpParasitol 2007.

40. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. J Infect Dis 2000;182Suppl 1:S62-8.

41. English JL, Hambidge KM. Plasma and serum zinc concentrations: Effect of time between collection and separation. ClinChimActa 1985;175:211-215.

42. Christian P, West KPJ, Khatry SK, et al. Vitamin A or beta-carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. J Nutr 2000;130:2675-2682.

43. West KP, Jr., Katz J, Khatry SK, et al. Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group.Bmj 1999;318:570-5.

44. Suharno D, West CE, Muhilal, Karyadi D, Hautvast JG. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. Lancet 1993;342:1325-8.

45. Schroeder SE, Reddy MB, Schalinske KL. Retinoic acid modulates hepatic iron homeostasis in rats by attenuating the RNA-binding activity of iron regulatory proteins. J Nutr 2007;137:2686-90.

46. Dijkhuizen MA, Wieringa FT, West CE, Muhilal. Zinc plus beta-carotene supplementation of pregnant women is superior to beta-carotene supplementation alone in improving vitamin A status in both mothers and infants. Am J ClinNutr 2004;80:1299-307.

47. Boron B, Hupert J, Barch DH, et al. Effect of zinc deficiency on hepatic enzymes regulating vitamin A status. J Nutr 1988;118:995-1001.

48. Stephensen CB. Vitamin A, infection, and immune function.Annu Rev Nutr 2001;21:167- 92.

49. Thurnham DI, Northrop-Clewes CA, McCullough FS, Das BS, Lunn PG. Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. J Infect Dis 2000;182Suppl 1:S23-8.