

REPORT ON THE WIC NUTRITION RISK CRITERION FOR HYPERTENSION IN PREGNANCY

Prepared for the US Department of Agriculture, Food and Nutrition Service

July 2007

James M. Roberts, MD
Professor of Obstetrics, Gynecology, and Reproductive Sciences and
Epidemiology
University of Pittsburgh Graduate School of Public Health
Magee-Womens Research Institute
Pittsburgh, PA

Lisa M. Bodnar, PhD, MPH, RD
Assistant Professor of Epidemiology and Obstetrics, Gynecology, and
Reproductive Sciences
University of Pittsburgh Graduate School of Public Health
Magee-Womens Research Institute
Pittsburgh, PA

Report on Nutrition Risk Criterion for Hypertension in Pregnancy

The purpose of this report is to present a concise evaluation of published literature on nutrition and risk of hypertensive disorders of pregnancy, focusing on preeclampsia. The final sections include responses to specific questions raised by the Risk Identification and Selection Collaborative (RISC).

BACKGROUND

The Hypertensive Disorders of Pregnancy

Increased blood pressure during pregnancy has long been recognized as identifying women and infants at increased risk. Hypertension in pregnancy is classified as chronic hypertension antedating pregnancy, or as hypertension appearing de novo in pregnancy (1). Hypertension with onset during pregnancy is classified as preeclampsia if accompanied by proteinuria, or gestational hypertension, pregnancy onset hypertension that is not accompanied by proteinuria. About 40% of cases of gestational hypertension will later develop proteinuria and be classified as preeclamptic. The remaining 60% do not develop proteinuria, and after pregnancy are classified as having transient hypertension of pregnancy.

These different forms of hypertension during pregnancy have very different risks for mother and baby. The most serious is preeclampsia, a syndrome present in 3 to 5% of pregnancies (2). In developing countries or those countries with absent or poor perinatal care, preeclampsia is associated with substantial maternal mortality. The cornerstone of perinatal care for preeclampsia relies on the fact that it is progressive, going from minimal to serious disease, and that it is a pregnancy specific syndrome that abates with delivery. Thus, with appropriate care a woman recognized as preeclamptic can be followed closely and delivered before the disorder progresses to put the mother at risk. However, even with good care, maternal morbidity can occur. Preeclampsia is a leading cause of ICU admissions for pregnant women (3). Additionally, the disease affects the infant, with a five-fold increase in perinatal mortality. Since delivery remains the only way to reverse the disease, premature delivery is sometimes the result of appropriate therapy. Delivery for preeclampsia accounts for 15% of all preterm births (4). Preterm birth is the leading cause of neonatal mortality and morbidity as well as neurological disability. In addition, in one third of the cases of preeclampsia the infant will not achieve its full growth potential and will be small for its gestational age (SGA) (5). SGA is associated with acute problems at birth but is also a precursor of later life cardiovascular disease, diabetes and obesity (6).

Hypertension that was present before delivery, termed chronic hypertension, increases perinatal mortality and morbidity, largely through an increased frequency of SGA infants. The major issue impact of chronic hypertension is that it is associated with an increased risk of preeclampsia. When preeclampsia occurs in a woman with chronic hypertension, which happens in about 20% of cases, this is termed superimposed

preeclampsia. It is the major factor leading to maternal and infant mortality and morbidity in these women (1).

Gestational hypertension, which does not progress to preeclampsia, presents minimal risk to mother or baby (1).

Preeclampsia sequelae

The risk of preeclampsia is highest in first pregnancies, 3-5%. However women who have been preeclamptic in a prior pregnancy have an increased risk of recurrence. This is about 20% overall, but varies from 10% in women with mild preeclampsia occurring at term to 40% in women with early onset severe preeclampsia (1). There is also an association of preeclampsia with later life cardiovascular disease. Women who have had preeclampsia are at increased risk compared with women who have had normal pregnancies. The greatest risk is in women who have had preeclampsia occurring early in pregnancy or who have had preeclampsia in more than one pregnancy (7, 8).

The Pathophysiology of Preeclampsia

Since preeclampsia is the major cause of morbidity in hypertensive pregnancies and since delivery is the only treatment and carries with it the attendant risk of prematurity, major efforts to affect outcome in preeclamptic women have been directed at an increased understanding of the disorder to facilitate prevention (9). In the last twenty years the understanding of the disease has increased greatly. It is clear that the important component of pregnancy that leads to preeclampsia is the placenta. One of the best lines of evidence supporting this is the relationship of the pregnancy complication, hydatidiform mole, and preeclampsia. Hydatidiform mole is a pregnancy abnormality in which only placental tissue develops without a fetus. In these pregnancies there is an excess of placental tissue, and not only does preeclampsia develop but it is more common and occurs earlier in pregnancy. Also supporting the fact that it is the excess of placental tissue that causes the preeclampsia in hydatidiform mole is the observation that there is not increased risk of preeclampsia in subsequent normal pregnancies. Once the placenta is delivered the disease will begin to abate. A major question is why the placenta leads to preeclampsia in some pregnancies while it does not in most pregnancies? This is proposed to be due to reduced blood flow to the placenta (9). This is usually secondary to abnormal placental implantation and failed remodeling of maternal blood vessel in the uterus that provide blood flow to the placenta. In normal pregnancy these vessels undergo striking changes, increasing in diameter by four fold and losing all of the smooth muscle from their walls. The result is increased blood flow to the placenta. This change does not occur in preeclampsia (10). In addition, it is thought that the reason chronic hypertension increases the risk of preeclampsia is that the maternal disease affects the vessels supplying the placenta as it does other vessels in the mother. Consistent with this, other maternal diseases that affect maternal blood vessels, such as diabetes and collagen vascular diseases increase the risk of preeclampsia. Also obstetric conditions with large placentas such as multiple gestations (twins, triplets etc.) also increase the risk of preeclampsia. In this setting it is felt there is relative reduction of blood flow since the very large placenta

cannot be adequately perfused. This has been referred to as Stage 1 of preeclampsia (9).

The pathological findings that comprise the maternal syndrome of preeclampsia are the manifestation of reduced perfusion of virtually all maternal organs. This is considered Stage 2 or preeclampsia with abnormal function of liver, kidney, brain as well as other organs and increased blood pressure. This is secondary to vasospasm, narrowing blood vessels and reducing organ blood flow, activation of the coagulation cascade with microthrombi blocking blood flow to organs, and loss of fluid from the intravascular space, further reducing blood flow. These three changes can all be explained by abnormal function of vascular endothelium that appears to be the predisposing factor for these changes (11). Of course the major question is how reduced blood flow to the placenta can result in reduced blood flow to all maternal organs. It is proposed that the reduced blood flow to the placenta leads to the production of materials that enter the maternal circulation to cause the maternal syndrome (11). The identification of this factor(s) is a major focus of preeclampsia research. Candidate molecules are cytokines, antiangiogenic factors, microparticles of placental trophoblast and oxidative stress. Oxidative stress is an excess of reactive oxygen species, known to be produced in settings of poor organ perfusion above that which can be buffered by the body's antioxidant defense systems. Theoretically maternal nutrition could have an impact at several levels. The lack of critical nutrients at the time of implantation could affect vascular remodeling or nutrient inadequacies could potentiate the formation of placental cytokines or result in inadequate buffering of maternal reactive oxygen species.

Nutrition as a factor in preeclampsia prevention.

Maternal nutritional status has long been hypothesized to have a role in the pathophysiology of preeclampsia (12), but only in the last decade has our understanding of the disorder's pathogenesis achieved a level adequate to provide testable hypotheses. It is now well understood that while preeclampsia is clinically evident late in pregnancy, the causal exposure(s) and many of the pathophysiological changes are present months earlier. Nonetheless, few studies have assessed dietary intake before clinically evident disease. Investigations have assessed nutrient intake late in pregnancy, and hypotheses have focused on the role of nutrition in Stage 2 of the disorder. No previous studies have rigorously examined dietary intake in periconceptual period, when nutritional status may affect implantation and/or vascular remodeling (Stage 1). Understanding of the role of periconceptual nutrition in the etiology of preeclampsia is particularly important since diet is modifiable. It is therefore obvious that preventing preeclampsia by identifying risk factors that can be modified in the prenatal period is paramount.

Energy and Macronutrients

Energy intake. We are aware of only one rigorous study to have examined energy intakes early among pregnant women who subsequently developed preeclampsia. Calusen et al (13) examined dietary intake by a food frequency questionnaire administered at 17-19 weeks gestation in 3771 Norwegian women. Energy intake was higher in women who went on to develop preeclampsia and highest

in preeclampsia occurring before 37 weeks (early-onset). The main difference between cases and controls was an increased intake of sucrose-containing soft drinks. Another study that is commonly cited when discussing nutrition and preeclampsia risk is one conducted by Morris et al. (14). These investigators administered one 24-hour dietary recall at 13-21 weeks gestation among 4157 women enrolled in a randomized controlled trial of calcium supplementation to prevent preeclampsia. Because calcium was not effective, treated and placebo patients were combined. The researchers found no difference in energy intake or any of the 28 nutrients compared among cases and controls. Nevertheless, this study was limited by the use of only one day of recall, which cannot capture usual dietary intake with good accuracy (15).

Protein. Despite the previously-held belief that low protein intake is associated with increased risk of preeclampsia (16), there have been no studies to indicate that low protein intake preceded the development of preeclampsia. The lack of a relation is supported by trials of protein supplementation that did not reduce the incidence of preeclampsia (17, 18).

Omega-3 polyunsaturated fatty acids (PUFAs). Some studies have shown a protective effect of omega-3 PUFAs on preeclampsia occurrence,(19-21) while others have found no association.(22-25). Confusing matters still are studies that found an increasing risk of preeclampsia in relation to high intake of total PUFA (omega-3 and omega-6),(13, 26) though these investigators did not separate the effects of omega-3 from omega-6 PUFAs. Olafsdottir and colleagues reported a U-shaped relation between omega-3 PUFA intake and risk of “hypertensive disorders of pregnancy” (i.e., gestational hypertension and preeclampsia), such that low and high intakes increased risk of adverse outcome (27). The conflicting results are possibly due to differing times of exposure assessment, methods of assessing and classifying PUFA intake, and definitions of preeclampsia. Furthermore, none of the previously published studies adjusted for intake of vitamin E or other antioxidants. PUFAs are highly susceptible to oxidation, and therefore the potential interaction between intake of PUFAs and antioxidants, and the confounding effects of antioxidant intake should be considered.

Trans-fatty acids. Preeclampsia and cardiovascular disease share many of the same pathophysiologic features. Thus, the strong association between high intake of *trans*-fatty acids and risk of cardiovascular disease (28-30), points to a potential role of *trans*-fats in preeclampsia. To our knowledge, only one study has examined *trans*-fatty acid status in relation to preeclampsia. Williams et al. (31) observed higher concentrations of *trans*-fatty acids in maternal erythrocytes compared to controls, but these data were cross-sectional and cannot determine if the elevated *trans*-fatty acid concentrations preceded disease onset. Dietary *trans*-fatty acid intake has not been studied.

Micronutrients

Dietary antioxidants. Recently, there has been increased interest in the role of antioxidant supplements in preeclampsia prevention. Extensive evidence accumulated over the last 30 years supports a role for oxidative stress in the pathogenesis of

preeclampsia (32). Observational data has demonstrated that low intakes of vitamin C and/or vitamin E are predictors of preeclampsia (33, 34). Yet, results of well-conducted randomized supplementation trials have been conflicting. In 1999, a small, randomized trial of antioxidant supplementation with 1000 mg vitamin C and 400 IU vitamin E or placebo initiated at 20 weeks' gestation among high-risk women reported a 61% reduction in the risk of preeclampsia (35). More recently, the Vitamins in Pre-eclampsia (VIP) trial, a randomized, double-blinded placebo-controlled trial of the same antioxidant therapy in a cohort of 2404 women with a range of clinical risk factors, found no difference in the incidence of preeclampsia among the treated or placebo groups (15% vs. 16%) (36). Moreover, the antioxidant group had a significantly higher incidence of perinatal complications, including low birth weight, gestational hypertension, and the need for medication therapies, than the placebo group. Soon after, results of a randomized trial of the same antioxidant therapy or placebo conducted in 1800 low-risk nulliparous women were reported (37). Again, no significant differences were observed between the vitamin and placebo groups on the risk of preeclampsia (6% versus 5%) or other primary outcomes. Ongoing trials of antioxidant therapy for the prevention of preeclampsia (a USA trial, a Brazil trial, and a multicenter WHO trial) will help clarify the efficacy and safety of high-dose antioxidants in pregnancy. An interesting feature of the USA trial that includes 10,000 women is that randomization occurred at 8-16 weeks rather than 18 weeks, as in the other studies. This may be important because in samples obtained taken at 18 weeks of the gestation, prior to any treatment in the VIP study, women with ascorbic acid in the lowest quartile for vitamin C concentration had twice the risk of preeclampsia.

The carotenoids (i.e., α -carotene, β -carotene, lycopene, lutein, and cryptoxanthin), are potent antioxidants, but have received little attention in the preeclampsia literature. Results of previous studies of maternal plasma carotenoid concentrations have been inconsistent, with some showing lower carotenoids in preeclamptic women (38-40), and others showing no difference (41). The cross-sectional nature of these studies, however, makes it impossible to know if such blood values preceded disease. In one small study of blood values before clinically evident disease, plasma β -carotene concentrations were not different by preeclampsia status (42). No previous studies have examined the relation between periconceptional or prenatal dietary carotenoid intake and risk of preeclampsia.

Folate. A link between folate and preeclampsia has been suggested since serum homocysteine concentrations are slightly higher in women destined to develop preeclampsia and markedly elevated in overt preeclampsia (43). Yet, studies of serum or plasma folate concentrations before or after the clinical onset of preeclampsia have been inconsistent (44-51). Similarly, folic acid supplementation has not conclusively been proven to have benefit for preeclampsia risk (52, 53).

Calcium. An inverse relation between calcium and preeclampsia has been documented in many epidemiologic and clinical studies (54-58). Low calcium intake was posited to be important for preeclampsia because of its ability to stimulate parathyroid hormone or renin release, thereby leading to vasoconstriction (55).

Although initial small calcium supplementation trials had promising results (59), other more recent trials have had mixed findings (60, 61). The most recent meta-analysis from the Cochrane Library summarizing supplementation trials of at least 1 g calcium for the prevention of preeclampsia reported a reduction in the risk of preeclampsia (12 trials, 15,206 women: RR 0.48, 95% CI 0.33, 0.69) (62). The most striking effects were seen among women at high-risk of developing preeclampsia (RR 0.22; 95% CI 0.12, 0.42) and women with low baseline dietary calcium intakes (RR 0.36; 95% CI 0.18, 0.70). This was tested in a recently completed trial by the WHO of calcium supplementation for pregnant populations known to have low calcium intake. Although there was not a significant reduction in the incidence of preeclampsia in the treated group, the frequency of serious outcomes (eclampsia and severe preeclampsia) was reduced significantly (about 30%) with calcium therapy (61).

Vitamin D. Vitamin D is a prohormone that is either ingested orally or is produced photochemically in the skin through exposure to sunlight. By far, the most important source of vitamin D is the skin's synthesis of the vitamin from casual exposure to sunlight (63). Vitamin D intake from diet and supplements is crucial to maintaining vitamin D status during limited sun exposure (64). Unfortunately, there are very few rich food sources of vitamin D (see table below) and most are rarely consumed (e.g., wild salmon, organ meats). Fortified foods (e.g., milk, breakfast cereal) and supplements are the largest contributors to vitamin D intake (65), but contain relatively little vitamin D compared with the amount experts believe necessary to prevent insufficiency (>1000 IU/d) (66). Not surprisingly, vitamin D deficiency is widespread among mothers and children (67, 68).

Source	Vitamin D content
<i>Natural sources</i>	
Exposure to UVB sunlight (20 min.)	6,000 IU
Salmon, wild (3.5 oz.)	600-1000 IU
Salmon, farmed (3.5 oz.)	100-250 IU
Sardines, canned (3.5 oz.)	~300 IU
Mackerel, canned (3.5 oz.)	~250 IU
Tuna, canned (3.6 oz.)	~230 IU
Cod liver oil (1 tsp)	400-1000 IU
Shiitake mushrooms, fresh (3.5 oz.)	100 IU
Egg yolk	~20 IU
<i>Fortified foods</i>	
Fortified milk (8 oz.)	~100 IU
Fortified orange juice (8 oz.)	~100 IU
Fortified breakfast cereal (per serving)	~100 IU
Infant formulas (8 oz.)	~100 IU
Fortified yogurts (8 oz.)	~100 IU
Fortified butter (3.5 oz.)	~50 IU
Fortified margarine (3.5 oz.)	~430 IU
Fortified cheeses (3 oz.)	~100 IU
<i>Supplements</i>	
Multivitamin	400 IU

Vitamin D may be important for preeclampsia prevention because its function is not limited to its effect on bone metabolism and mineral homeostasis (69). Vitamin D is known to regulate genes associated with normal implantation and angiogenesis (70). It has immunomodulatory properties (71, 72), influences vascular structure and function (73), and regulates blood pressure (74). Maternal vitamin D deficiency may also predispose to the increased inflammatory response that characterizes preeclampsia (71, 72).

We conducted the first study examining maternal vitamin D status before disease onset and risk of preeclampsia (75). In a nested case-control study of nulliparous pregnant women in Pittsburgh who enrolled at <16 weeks gestation, we selected all preeclampsia cases (n=55) and a random sample of controls (n=219). We observed that adjusted serum 25(OH)D levels at <22 weeks gestation were lower in women who subsequently developed preeclampsia compared with controls (geometric mean (95% CI): 53.1 (47.1, 59.9) versus 45.4 (38.6, 53.4) nmol/l, p<0.01). There was a monotonic dose-response relation between serum 25(OH)D at <22 weeks and risk of preeclampsia. After confounder adjustment, a 50-nmol/l decline in 25(OH)D concentration doubled the risk of preeclampsia (adjusted OR (95% CI): 2.4 (1.1, 5.4)). Moreover, newborns of preeclamptic mothers were twice as likely as control newborns to have 25(OH)D <37.5 nmol/l (adjusted OR (95% CI): 2.2 (1.2, 4.1)). These data suggest that maternal vitamin D deficiency may be an independent risk factor for preeclampsia.

Our findings are supported by results from two vitamin D supplementation studies to prevent preeclampsia. In an uncontrolled trial conducted in 1938, treatment with a supplement containing 900 IU/d vitamin D provided at 20 weeks' gestation reduced the odds of PE by 32% (95% CI: 11-47%) (76). Marya et al. randomized 400 women at 20-24 weeks' gestation to vitamin D (1,200 IU/day) and calcium (375 mg/day) supplements or no treatment and found a significant reduction in blood pressure (p<0.001) and a non-significant reduction in preeclampsia incidence in the treated group compared with the untreated (6% vs. 9%) (77). Data from calcium trials in preeclampsia may also be relevant to the effect of vitamin D on disease risk. Calcium prevents preeclampsia among women with very low baseline calcium intake (62). Inadequate dietary intake of calcium can cause a secondary vitamin D deficiency (78). Thus, calcium supplementation may increase the available vitamin D for its hypothesized effect on angiogenesis, vascular physiology, and insulin sensitivity (79).

Zinc. Biomarkers of zinc status, including plasma and white cell zinc concentrations and placental zinc concentrations are reduced in women with overt gestational hypertension and/or preeclampsia compared with controls (80-83). Zinc has not been assessed in observational studies before disease onset. One randomized trial of zinc supplementation during pregnancy showed a protective effect against the development of preeclampsia (84), while the other had no benefit (85). Both studies were underpowered to test this effect. More research is needed into the role of zinc in the pathogenesis of preeclampsia.

Magnesium. Because magnesium sulfate has been used to successfully treat and prevent eclampsia, there has been some research into the role of dietary magnesium as a risk factor for preeclampsia. However, in the two randomized trials conducted to evaluate elemental magnesium supplementation to prevent preeclampsia, no benefits were observed (86, 87).

Salt intake. Although excessive salt intake may be related to hypertension outside the context of pregnancy, there is very little evidence to support an association between salt and risk of preeclampsia or gestational hypertension. There was widespread use of salt restriction during pregnancy in the recent past. However, a thorough evaluation conducted in 1990 (88) showed no definitive evidence that sodium intake is related to incidence of the disorder. Subsequent randomized trials conducted to restrict salt intake during pregnancy had no benefit (89, 90).

Multivitamin supplements. In a recent report, we showed that regular use of prenatal or multivitamins in the 3 months before conception and 3 months after conception reduced the risk of preeclampsia by 45% (RR 0.55; 95% CI: 0.32, 0.95), even after adjustment for sociodemographic and lifestyle variables (91). These results are consistent with another observational study of multivitamin use during pregnancy (92, 93) and a uncontrolled trial of multivitamins provided at 20 weeks' gestation (20). Past studies assessed typical multivitamins, which contain doses of nutrients around the daily recommended levels in pregnancy. While the leading evidence suggests that antioxidants or folate in the multivitamins may be the most relevant for this effect, many other micronutrients have been implicated and warrant further study (94).

Summary: strength of the evidence relating nutrients to preeclampsia prevention. The strongest evidence relating nutrients to preeclampsia prevention is for vitamins C, E and calcium. Each of these nutrients has been well-tested in randomized controlled trials, the findings of which are supported by rigorous observational studies. It seems clear so far that 1 g of calcium may prevent preeclampsia only in women at high risk of the disease and among women with very low baseline calcium intake. Vitamins C and E in the form of high-dose supplements may prevent preeclampsia as well, but we are awaiting a very large randomized trial in the U.S. and two other trials world-wide to determine if supplementation may prevent disease and in what population. It is important to recognize that the dosages tested in these studies are well above the amount achieved through a usual diet.

For other nutrients, the evidence is currently not strong enough to use as the basis for specific recommendations. While there are some intriguing observational data and strong biologic plausibility for a role of nutrients like folic acid, vitamin D, and omega-3 fatty acids, more rigorous studies are needed to test these associations definitively. While evidence from the diet-cardiovascular disease literature can help us generate hypotheses as to nutrients that may be relevant, it is clear that more rigorous studies, particularly as they relate to dietary intake of nutrients (rather than supplementation only) are desperately needed.

Prepregnancy obesity and preeclampsia risk.

One of the most consistent risk factors for preeclampsia is maternal prepregnancy obesity. Investigators of numerous studies have reported that women who enter pregnancy with a high prepregnancy body mass index (BMI) are significantly more likely than leaner women to develop preeclampsia (95-99). Recently, we demonstrated a monotonic, dose-response relation between prepregnancy BMI and risk of both severe and mild preeclampsia and severe and mild transient hypertension of pregnancy (95). For instance, compared with white women with a BMI of 20, the odds ratios (95% confidence interval) for severe preeclampsia at BMI values of 25 and 30 were 1.7 (1.1, 2.5) and 3.4 (2.1, 5.6) in white women, and 2.1 (1.4, 3.2) and 3.2 (2.1, 5.0) in black women, respectively. With a 30% prevalence of obesity among childbearing-aged women in the United States, obesity could account for over 30% of cases.

Despite the fact that obesity is associated with positive energy balance, micronutrient deficiencies are also present. Numerous studies of non-pregnant populations have found inadequate micronutrient concentrations in particular antioxidants in obese women (100, 101). We have confirmed similar findings in obese pregnant women with ascorbate (Bodnar, unpublished 2007). Vitamin C and other antioxidant concentrations decrease with increasing BMI. Fructose intake is proposed as important in the generation of the metabolic syndrome. A major source of dietary fructose is soft drinks. In years past sucrose was used to sweeten soft drinks. Sucrose is metabolized to fructose and glucose. Since the 1970's high fructose corn syrup has largely replaced sucrose and thus contributes directly to fructose intake. Obese individuals report a high intake of soft drinks (102).

Physical activity in preeclampsia prevention.

A number of investigations into the role of leisure-time physical activity in the pathogenesis of preeclampsia have been recently published, with promising benefits of exercise on disease risk. In a case-control study of 172 women who later developed preeclampsia and 505 controls residing in Quebec City and Montreal, Marcoux and colleagues found that women who reported performing regular recreational physical activity in the first half of pregnancy were less likely to develop preeclampsia, even after controlling for work activity and other confounders (103). There was a dose-response association observed, with decreasing risks as the average amount of time in exercise increased. Similar findings were reported in another case-control study conducted in Washington State (104). Saftlas and colleagues avoided the concerns about recall bias by conducting a prospective cohort study of 2638 pregnant women in New Haven, Connecticut who were interviewed at <16 weeks' gestation (105). Leisure-time physical activity had a protective effect on preeclampsia risk that was similar in magnitude to the aforementioned case-control studies. Others have observed that women who reported very strenuous to maximal exertion during usual prepregnancy physical activity were 78% less likely to develop preeclampsia (OR 0.22; 95% CI 0.11, 0.44) than women who reported negligible or minimal exertion (106). Taken together, these results strongly suggest that a physical activity intervention may reduce the risk of preeclampsia.

RESPONSE TO QUESTIONS RAISED BY THE RISC WORKGROUP

1. What is the general consensus regarding preeclampsia as it relates to pregnant and postpartum women?

Preeclampsia is a major pregnancy abnormality in developed and developing countries. Maternal mortality is largely preventable by good prenatal care with delivery for progressive disease. The absence of prenatal care is largely responsible for the 50,000 deaths occurring yearly in developing countries. Good prenatal care prevents most maternal deaths. However, preeclampsia even with good care increases risk for babies. Preeclampsia directly affects the baby by reducing the delivery of blood and nutrients to the baby. In addition, the appropriate management of preeclampsia, delivering sick mothers with preeclampsia to prevent worsening of the disease, will result in early delivery with preterm birth in 10% of cases. There is no treatment once the disease is manifest, and the ideal approach would be prevention.

Preeclampsia appears to be a marker of later life cardiovascular disease (9). Cardiovascular disease is more common in women who have had preeclampsia, and the general consensus is that this is because preeclampsia is at least in part due to the same factors that lead to later life cardiovascular disease. Despite this, preeclampsia is not a subject for major research funding and has not attracted a great deal of national attention. This is problematic, as good prenatal care, which is the cornerstone of current management, would be greatly aided by public awareness. Furthermore, it is one of the few factors in women that provide evidence of later life cardiovascular risk. Knowledge of preeclampsia may stimulate healthy lifestyle and primary cardiovascular disease prevention. It is also quite possible that these same healthy lifestyle factors, including diet, will reduce the recurrence of the disorder.

2a. For a pregnant woman diagnosed with preexisting chronic hypertension, what nutrition guidance would be considered appropriate?

Although pregnant women with chronic hypertension are clearly a group at high risk of developing preeclampsia and other adverse outcomes of pregnancy, there has been very little research related to nutritional adjustments during gestation in this population. Salt restriction is an important component of managing hypertension in nonpregnant individuals, but is less so for pregnancy. In fact, the normal physiologic plasma volume expansion of pregnancy may be jeopardized with extremely low sodium intakes (≤ 2 g NaCl) (107). It is acceptable to use reduced sodium diets in pregnancy among women whose "salt-sensitive" hypertension was successfully managed with such a diet before conception. The sodium restriction should be limited to 60-80 mEq/d. There is equivocal evidence as to whether calcium supplementation may prevent preeclampsia. Meta-analyses suggest that only women with extremely low baseline calcium intakes will benefit (62). Other nutritional interventions, such as supplementation with dietary antioxidants (vitamin C and vitamin E) also show promise in some populations (35). However, calcium and antioxidant supplementation have not been specifically studied in pregnant women with chronic hypertension. Other observational data suggest that regular use of a prenatal vitamin or multivitamin around the time of conception may

lower risk of preeclampsia in a general obstetric population (91). Again, whether this association applies to pregnant women with chronic hypertension is unknown.

We believe that until other information becomes available, it is entirely appropriate for pregnant women with chronic hypertension to follow nutrition guidelines established for all pregnant women. Women should (1) take a prenatal vitamin before conception and throughout gestation (91); (2) eat a diet that follows the Dietary Guidelines for Americans (108); and (3) eat at least 3 meals and 2 snacks per day as outlined by ACOG (109).

2b. For a pregnant woman diagnosed with preexisting chronic hypertension, would the weight gain recommendation be different from those currently in use?

There are no published data evaluating weight gain as it relates to adverse outcomes in women with chronic hypertension. Thus, the current IOM guidelines for weight gain based on pre-pregnancy body mass index should be followed until the IOM recommendations are revised or new information becomes available. As for all pregnant women, it should be stressed to women with chronic hypertension that it is undesirable to gain excessive gestational weight or lose weight during pregnancy (even among women entering pregnancy obese) (107).

Although it has been suggested that extremely vigorous activity may be a problem for women with chronic hypertension in pregnancy (107), moderate exercise should provide the same advantages to women with chronic hypertension during pregnancy as it does to other pregnant women (103).

3a. For a pregnant woman diagnosed with preeclampsia, what nutrition guidance would be considered appropriate? Are certain nutrients recommended at levels greater than the RDA for pregnancy? Would the weight gain recommendation be different from the current guidelines established by the IOM?

When addressing the nutritional issues in women diagnosed with preeclampsia, it is important to understand how the disorder is managed. Women with overt preeclampsia are followed quite closely with delivery for worsening disease or to avoid worsening disease if the pregnancy is near term. Thus, it is rare for women with preeclampsia to remain pregnant long after the diagnosis. It is important to note that delivery is the only known cure for preeclampsia. Patients with mild preeclampsia may progress slowly and be followed but this is unusual. Women with severe disease and a very immature infant are sometimes followed extremely closely in a hospital setting.

In the management of patients with diagnosed preeclampsia, there are very few nutritional issues to consider. It is recommended that women receive the recommended level of energy, protein, and sodium; intakes should neither be too low nor excessive.

3d. For a pregnant woman diagnosed with preeclampsia, are lifestyle practices, such as moderate exercise, contraindicated?

Reduced physical activity throughout the day for a pregnant woman diagnosed with preeclampsia is thought to be beneficial, but this recommendation has not been proven in rigorous studies.

3e. For a pregnant woman diagnosed with preeclampsia, how might the WIC foods be helpful?

To women diagnosed with preeclampsia, WIC foods would be beneficial in ensuring that women have access to adequate sources of energy and protein.

3f. For a pregnant woman diagnosed with preeclampsia, would verbal encouragement to keep all prenatal care appointments be helpful? What additional information may be helpful?

Women with overt or severe preeclampsia are managed in the hospital. Women with mild preeclampsia or women without overt hypertension but in whom preeclampsia is suspected would benefit from encouragement to keep all prenatal care appointments. Management of the disorder is primarily based on increased surveillance at prenatal care visits. Increased surveillance helps to prevent the disorder from worsening and to protect the health of the fetus.

4a. For a postpartum woman who had preeclampsia while pregnant, what advice might help lower her risk of a reoccurrence in a future pregnancy?

An important component of preeclampsia management that has not received adequate attention is health maintenance between pregnancies and attempts to prepare for the next pregnancy. Although nutritional prevention of preeclampsia is difficult to prove, all of the potentially effective dietary modifications are components of an appropriate, healthy diet. There is evidence that excessive weight gain between pregnancies is associated with an increased risk of preeclampsia in subsequent pregnancies (110). In addition, an excessive intake of fructose in soft drinks may contribute to obesity (111) and is specifically associated with metabolic changes known to predispose to preeclampsia and associated with later life cardiovascular disease (112). Higher blood vitamin C concentrations in early pregnancy are associated with a reduced risk of preeclampsia (113), and a diet high in fruits and vegetables (rich sources of vitamin C) is a dietary recommendation for all adults (108). Similarly, a diet with adequate calcium is recommended for reproductive age women (108) and this might also be beneficial to prevent preeclampsia (114). Thus, women who have had preeclampsia should be advised that they are at risk for recurrent disease and also for later life cardiovascular disease. They should be informed that a valuable aid in preventing these sequelae is a nutritionally adequate diet.

In summary, we recommend the following nutrition guidance for preeclampsia prevention:

- **Consume a diet consistent with the Dietary Guidelines for Americans.**

- **Meet RDAs for macro- and micronutrients.**
- **Take a prenatal vitamin daily.**
- **Regularly engage in physical activity.**
- **Aim for a healthy BMI before conception.**
- **Avoid excessive weight gain during pregnancy and between pregnancies.**

4b. Would advice about the DASH diet be helpful?

There is no data to support the DASH diet (high fruit and vegetable intake along with low-fat dairy intake) in reducing recurrence of preeclampsia. It does lower blood pressure (115) and by and large is compatible with the usual recommendations regarding a healthy diet, as suggested by the Dietary Guidelines (108). However, specific recommendation of this diet is not currently justified for the prevention of preeclampsia.

4c. What levels of calcium, vitamin C, vitamin E, and folic acid/folate could be recommended?

Currently there is no evidence to support doses of vitamins C and E prior to or during pregnancy that are higher than the RDA. There is observational data to suggest an adequate intake of vitamin C in early pregnancy protects against preeclampsia (34). Also, observational studies suggest standard vitamin supplements taken before pregnancy reduces the risk of preeclampsia (91). Like all observational data, these are limited by potential misclassification, recall bias, and unmeasured confounding. However, they support the notion that intake of vitamins C and E, either from foods or supplements, in amounts at the RDA for pregnant women, may protect against preeclampsia.

There is inconsistent evidence supporting folic acid in the pathophysiology of preeclampsia. Because it is well established that 400 ug of folic acid taken periconceptionally will reduce the risk of neural tube defects, women should strive for this level of supplementation while also meeting the RDA for folate from food sources.

In settings of markedly and chronically reduced calcium intake, calcium supplementation may reduce preeclampsia risk (61). This has been directly tested in US women with normal and low calcium intake as measured by urinary calcium excretion and did not reduce the risk of preeclampsia (116). Usual pregnancy recommendations for calcium intake appear adequate in developed countries.

4d. What lifestyle practices, such as exercise could be recommended?

Women who have had preeclampsia should strive to return to prepregnancy weight both for benefit in future pregnancies and as an aid to later life cardiovascular health (110, 117). Also, it appears that mild to moderate exercise prior to pregnancy is beneficial to reduce the risk of preeclampsia in subsequent pregnancies (103, 105, 106).

Furthermore, beginning such a program has established benefit for later cardiovascular benefit in these high-risk women.

Smoking should be discouraged. The relationship of smoking to preeclampsia is complex with a reduced risk of preeclampsia in women who smoke during pregnancy (118). However, when preeclampsia occurs in smokers, it is of greater severity (119). There is no question that smoking increases virtually every other adverse pregnancy outcome: preterm birth, abortion, ectopic pregnancy, abruptio placenta (120) and growth restriction (121). Furthermore, it is detrimental to later life cardiovascular health.

4e. What is the relationship between the metabolic syndrome and preeclampsia?

The metabolic syndrome, a precursor of later life cardiovascular disease, predisposes to preeclampsia and is accentuated by preeclampsia. In the metabolic syndrome, insulin resistance is increased with consequent abnormal circulating lipids, increased uric acid and hypertension. Preeclampsia is more common in women with the metabolic syndrome (122). Additionally, the metabolic abnormalities associated with preeclampsia mimic those of the metabolic syndrome. It would seem that the metabolic syndrome increases the risk of preeclampsia and contributes to the pathophysiology of the condition. Not surprisingly women who have had preeclampsia are more likely to manifest the metabolic syndrome in the years after pregnancy (123).

4f. Does preeclampsia raise a woman's risk for future cardiovascular disease and Type 2 diabetes? If yes, what advice could be given to help reduce this risk?

Women with preeclampsia have a clearly established increased risk of cardiovascular disease in later life. The risk for type 2 diabetes is less well-established. There are no studies that specifically determined lifestyle risk factors for cardiovascular disease and diabetes in women with preeclampsia. However, we expect the prudent advice is the same as it would be for all women aiming to reduce chronic disease risk: a diet that follows the Dietary Guidelines for Americans, avoidance of obesity, increased physical activity and no smoking.

Special considerations in chronic hypertension:

5a. Are there any nutrient-drug interactions with the drugs commonly used for treating hypertension during pregnancy (i.e., beta blockers and methyldopa)? If so, what are they?

There are no reports of nutritional drug interactions with any of the drugs usually used to treat women with hypertension.

5b. Are these treatments different for breastfeeding mothers?

There is very little information on nursing and antihypertensive therapy. All of the usual antihypertensive drugs transfer into breast milk, so all are of some concern. Not all

drugs get into breast milk to the same extent and this has influenced the choice of drugs to use in nursing mothers. Beta-blockers have been studied more than most drugs. They have widely differing transfer into milk. The beta adrenergic antagonists: metoprolol, nadolol, acebutolol, sotalol, and atenolol are very well transferred while other agents, oxprenolol and propranolol are minimally transferred. However, an extremely important point is that the amount of drugs delivered to the baby in breast milk for even the drugs transferred to the highest extent does not approach therapeutic doses for infants. Other commonly used antihypertensive drugs, calcium channel blockers and alpha-methyl dopa are minimally transferred in milk. Compounding the difficulty in selecting an agent rationally for a nursing mother is the fact that ACE inhibitors are among the least transferred, but have reported risk for fetuses and neonates. They are probably best avoided. Current recommendations are that if beta adrenergic antagonists are chosen, the drugs with least transfer should be used, and that of other classes of drugs alpha-methyl dopa and calcium channel blockers are likely safe. Not surprisingly there is controversy about the use of ACE inhibitors. Nonetheless all of the recommendations are based on little data and there is absolutely no long range follow-up.

5c. Is there a relationship between breastfeeding and hypertension in which breastfeeding ameliorates hypertension in women, especially over the long term?

There is no known evidence that nursing reduces maternal blood pressure. There may be a moderate effect to lower systolic blood pressure in adults breast fed as infants (124).

REFERENCES

1. Gifford RW, August PA, Cunningham G, Green LA, Lindheimer MD, McNellis D, Roberts JM, Sibai BM, Taler SJ. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American Journal of Obstetrics and Gynecology* 2000; 183(1): S1-S22.
2. Roberts JM. Pregnancy related hypertension. In: *Maternal Fetal Medicine*. Creasy RK, Resnik R, ed. Philadelphia: W.B. Saunders 1998: 883-872.
3. Tang LC, Kwok AC, Wong AY, Lee YY, Sun KO, So AP. Critical care in obstetrical patients: an eight-year review. *Chinese Medical Journal* 1997; 110(12): 936-41.
4. Goldenberg RL, Rouse DJ. Prevention of premature birth. *N Engl J Med* 1998; 339(5): 313-20.
5. Eskenazi B, Fenster L, Sidney S, Elkin EP. Fetal growth retardation in infants of multiparous and nulliparous women with preeclampsia. *Am J Obstet Gynecol* 1993; 169(5): 1112-8.
6. Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *International Journal of Epidemiology* 2002; 31(6): 1235-9.
7. Chesley LC, Annitto JE, Cosgrove RA. The remote prognosis of eclamptic women. *American Journal of Obstetrics and Gynecology* 1975; 124(5): 446-59.
8. Funai EF, Friedlander Y, Paltiel O, Tiram E, Xue X, Deutsch L, Harlap S. Long-term mortality after preeclampsia. *Epidemiology* 2005; 16(2): 206-15.
9. Roberts JM, Gammill HS. Preeclampsia: recent insights. *Hypertension* 2005; 46(6): 1243-9.
10. Pijnenborg R, Vercruyssen L, Hanssens A. The uterine spiral arteries in human pregnancy: Facts and controversies. *Placenta* 2006; 27(9-10): 939-958.
11. Gammill HS, Roberts JM. Emerging concepts in preeclampsia investigation. *Frontiers in Bioscience* 2007; 12: 2403-11.
12. Chesley LC, *Hypertensive disorders of pregnancy*. 1978, New York: Appleton-Century-Crofts.
13. 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(2): 451-8.
14. Morris CD, Jacobson SL, Anand R, Ewell MG, Hauth JC, Curet LB, Catalano PM, Sibai BM, Levine RJ. Nutrient intake and hypertensive disorders of pregnancy: Evidence from a large prospective cohort. *Am J Obstet Gynecol* 2001; 184(4): 643-51.
15. Willet WC, *Nutritional Epidemiology*. 2nd ed. 1998, New York: Oxford University Press.
16. Brewer T. Nutrition and preeclampsia. *Obstet Gynecol* 1969; 33(3): 448-9.
17. Herrera JA, Arevalo-Herrera M, Herrera S. Prevention of preeclampsia by linoleic acid and calcium supplementation: a randomized controlled trial. *Obstet Gynecol* 1998; 91(4): 585-90.
18. Mardones-Santander F, Rosso P, Stekel A, Ahumada E, Llaguno S, Pizarro F, Salinas J, Vial I, Walter T. Effect of a milk-based food supplement on maternal nutritional status and fetal growth in underweight Chilean women. *Am J Clin Nutr* 1988; 47(3): 413-9.

19. Dyerberg J, Bang HO. Pre-eclampsia and Prostaglandins. *Lancet* 1985(June 1, 1985): 1267.
20. Olsen SF, Secher NJ. A possible preventive effect of low-dose fish oil on early delivery and pre-eclampsia: indications from a 50-year-old controlled trial. *Br J Nutr* 1990; 64(3): 599-609.
21. Williams MA, Zingheim RW, King IB, Zebelman AM. Omega-3 fatty acids in maternal erythrocytes and risk of preeclampsia. *Epidemiology* 1995; 6(3): 232-7.
22. Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. *Br J Obstet Gynaecol* 1995; 102(2): 123-6.
23. Kesmodel U, Olsen SF, Salvig JD. Marine n-3 fatty acid and calcium intake in relation to pregnancy induced hypertension, intrauterine growth retardation, and preterm delivery. A case-control study. *Acta Obstet Gynecol Scand* 1997; 76(1): 38-44.
24. Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. *Br J Obstet Gynaecol* 2000; 107(3): 382-95.
25. Salvig JD, Olsen SF, Secher NJ. Effects of fish oil supplementation in late pregnancy on blood pressure: a randomised controlled trial. *Br J Obstet Gynaecol* 1996; 103(6): 529-33.
26. Scholl TO, Leskiw M, Chen X, Sims M, Stein TP. Oxidative stress, diet, and the etiology of preeclampsia. *Am J Clin Nutr* 2005; 81(6): 1390-6.
27. Olafsdottir AS, Magnusardottir AR, Thorgeirsdottir H, Hauksson A, Skuladottir GV, Steingrimsdottir L. Relationship between dietary intake of cod liver oil in early pregnancy and birthweight. *Bjog* 2005; 112(4): 424-9.
28. Willett WC, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Rosner BA, Sampson LA, Hennekens CH. Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet* 1993; 341(8845): 581-5.
29. Oomen CM, Ocke MC, Feskens EJ, van Erp-Baart MA, Kok FJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet* 2001; 357(9258): 746-51.
30. Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* 1997; 145(10): 876-87.
31. Williams MA, King IB, Sorensen TK, Zingheim RW, Troyer BL, Zebelman AM, Luthy DA. Risk of preeclampsia in relation to elaidic acid (trans fatty acid) in maternal erythrocytes. *Gynecol Obstet Invest* 1998; 46(2): 84-7.
32. Hubel CA. Oxidative stress and preeclampsia. *Fetal and Maternal Medicine Review* 1997; 9: 73-101.
33. Rumbold A, Duley L, Crowther C, Haslam R. Antioxidants for preventing pre-eclampsia. *Cochrane Database Syst Rev* 2005(4): CD004227.

34. Zhang C, Williams MA, King IB, Dashow EE, Sorensen TK, Frederick IO, Thompson ML, Luthy DA. Vitamin C and the risk of preeclampsia--results from dietary questionnaire and plasma assay. *Epidemiology* 2002; 13(4): 409-16.
35. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, Parmar K, Bewley SJ, Shennan AH, Steer PJ, Poston L. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999; 354(9181): 810-6.
36. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006; 367(9517): 1145-54.
37. Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006; 354(17): 1796-806.
38. Mikhail MS, Anyaegbunam A, Garfinkel D, Palan PR, Basu J, Romney SL. Preeclampsia and antioxidant nutrients: decreased plasma levels of reduced ascorbic acid, alpha-tocopherol, and beta-carotene in women with preeclampsia. *Am J Obstet Gynecol* 1994; 171(1): 150-7.
39. Palan PR, Mikhail MS, Romney SL. Placental and serum levels of carotenoids in preeclampsia. *Obstet Gynecol* 2001; 98(3): 459-62.
40. Ziari SA, Mireles VL, Cantu CG, Cervantes M, 3rd, Idrisa A, Bobsom D, Tsin AT, Glew RH. Serum vitamin A, vitamin E, and beta-carotene levels in preeclamptic women in northern nigeria. *Am J Perinatol* 1996; 13(5): 287-91.
41. Zhang C, Williams MA, Sanchez SE, King IB, Ware-Jauregui S, Larrabure G, Bazul V, Leisenring WM. Plasma concentrations of carotenoids, retinol, and tocopherols in preeclamptic and normotensive pregnant women. *Am J Epidemiol* 2001; 153(6): 572-80.
42. Jendryczko A, Drozd M. Plasma retinol, beta-carotene and vitamin E levels in relation to the future risk of pre-eclampsia. *Zentralbl Gynakol* 1989; 111(16): 1121-3.
43. Mignini LE, Latthe PM, Villar J, Kilby MD, Carroli G, Khan KS. Mapping the theories of preeclampsia: the role of homocysteine. *Obstet Gynecol* 2005; 105(2): 411-25.
44. Cotter AM, Molloy AM, Scott JM, Daly SF. Elevated plasma homocysteine in early pregnancy: a risk factor for the development of severe preeclampsia. *Am J Obstet Gynecol* 2001; 185(4): 781-5.
45. Cotter AM, Molloy AM, Scott JM, Daly SF. Elevated plasma homocysteine in early pregnancy: a risk factor for the development of nonsevere preeclampsia. *Am J Obstet Gynecol* 2003; 189(2): 391-4; discussion 394-6.
46. Hogg BB, Tamura T, Johnston KE, Dubard MB, Goldenberg RL. Second-trimester plasma homocysteine levels and pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction. *Am J Obstet Gynecol* 2000; 183(4): 805-9.
47. Powers RW, Evans RW, Majors AK, Ojimba JI, Ness RB, Crombleholme WR, Roberts JM. Plasma homocysteine concentration is increased in preeclampsia and is associated with evidence of endothelial activation. *Am J Obstet Gynecol* 1998; 179(6 Pt 1): 1605-11.
48. Rajkovic A, Catalano PM, Malinow MR. Elevated homocyst(e)ine levels with preeclampsia. *Obstet Gynecol* 1997; 90(2): 168-71.

49. Rajkovic A, Mahomed K, Malinow MR, Sorenson TK, Woelk GB, Williams MA. Plasma homocyst(e)ine concentrations in eclamptic and preeclamptic African women postpartum. *Obstet Gynecol* 1999; 94(3): 355-60.
50. Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: A systematic review. *Placenta* 1999; 20(7): 519-29.
51. Sanchez SE, Zhang C, Malinow MR, Ware-Jauregui S, Larrabaure G, Williams MA. Plasma folate, vitamin B12, and homocyst(e)ine concentrations in preeclamptic and normotensive Peruvian women. *Am J Epidemiol* 2001; 153(5): 474-80.
52. Charles DH, Ness AR, Campbell D, Smith GD, Whitley E, Hall MH. Folic acid supplements in pregnancy and birth outcome: re-analysis of a large randomised controlled trial and update of Cochrane review. *Paediatr Perinat Epidemiol* 2005; 19(2): 112-24.
53. Mahomed K. Folate supplementation in pregnancy. *Cochrane Database Syst Rev* 2000(2): CD000183.
54. Belizan JM, Villar J. The relationship between calcium intake and edema-, proteinuria-, and hypertension-gestosis: an hypothesis. *Am J Clin Nutr* 1980; 33(10): 2202-10.
55. Belizan JM, Villar J, Repke J. The relationship between calcium intake and pregnancy-induced hypertension: up-to-date evidence. *Am J Obstet Gynecol* 1988; 158(4): 898-902.
56. Hamlin RH. The prevention of eclampsia and pre-eclampsia. *Lancet* 1952; 1(2): 64-8.
57. Repke JT, Villar J. Pregnancy-induced hypertension and low birth weight: the role of calcium. *Am J Clin Nutr* 1991; 54(1 Suppl): 237S-241S.
58. Villar J, Belizan JM, Fischer PJ. Epidemiologic observations on the relationship between calcium intake and eclampsia. *Int J Gynaecol Obstet* 1983; 21(4): 271-8.
59. Bucher HC, Guyatt GH, Cook RJ, Hatala R, Cook DJ, Lang JD, Hunt D. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *Jama* 1996; 275(14): 1113-7.
60. Levine RJ, Esterlitz JR, Raymond EG, DerSimonian R, Hauth JC, Ben Curet L, Sibai BM, Catalano PM, Morris CD, Clemens JD, Ewell MG, Friedman SA, Goldenberg RL, Jacobson SL, Joffe GM, Klebanoff MA, Petrusis AS, Rigau-Perez JG. Trial of Calcium for Preeclampsia Prevention (CPEP): rationale, design, and methods. *Control Clin Trials* 1996; 17(5): 442-69.
61. Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N, Purwar M, Hofmeyr J, Nguyen TN, Campodonico L, Landoulsi S, Carroli G, Lindheimer M. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. *Am J Obstet Gynecol* 2006; 194(3): 639-49.
62. Hofmeyr GJ, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2006; 3: CD001059.
63. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004; 79(3): 362-71.
64. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr* 2004; 80(6 Suppl): 1710S-6S.
65. Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. *J Nutr* 2005; 135(10): 2478-85.

66. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, Holick MF, Hollis BW, Lamberg-Allardt C, McGrath JJ, Norman AW, Scragg R, Whiting SJ, Willett WC, Zittermann A. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007; 85(3): 649-50.
67. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357(3): 266-81.
68. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr* 2007; 137(2): 447-52.
69. DeLuca HF. The vitamin D story: a collaborative effort of basic science and clinical medicine. *FASEB J* 1988; 2(3): 224-36.
70. Daftary GS, Taylor HS. Endocrine regulation of HOX genes. *Endocrine Reviews* 2006; 27(4): 331-55.
71. Hewison M. Vitamin D and the immune system. *J Endocrinol* 1992; 132(2): 173-5.
72. Rigby WF. The immunobiology of vitamin D. *Immunology Today* 1988; 9(2): 54-8.
73. Braam LA, Hoeks AP, Brouns F, Hamulyak K, Gerichhausen MJ, Vermeer C. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. *Thromb Haemost* 2004; 91(2): 373-80.
74. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; 110(2): 229-38.
75. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab* 2007; 92(9): 3517-22.
76. People's League of Health. The nutrition of expectant and nursing mothers in relation to maternal and infant mortality and morbidity. *J Obstet Gynaecol Br Emp* 1946; 53: 498-509.
77. Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxemia of pregnancy. *Gynecol Obstet Invest* 1987; 24(1): 38-42.
78. Wharton B, Bishop N. Rickets. *Lancet* 2003; 362(9393): 1389-400.
79. Hypponen E. Vitamin D for the prevention of preeclampsia? A hypothesis. *Nutr Rev* 2005; 63(7): 225-32.
80. Acikgoz S, Harma M, Harma M, Mungan G, Can M, Demirtas S. Comparison of angiotensin-converting enzyme, malonaldehyde, zinc, and copper levels in preeclampsia. *Biol Trace Elem Res* 2006; 113(1): 1-8.
81. Adam B, Malatyalioglu E, Alvur M, Talu C. Magnesium, zinc and iron levels in pre-eclampsia. *J Matern Fetal Med* 2001; 10(4): 246-50.
82. Lao TT, Chin RK, Swaminathan R, Mak YT. Plasma and erythrocyte zinc concentrations in pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 1989; 30(2): 117-22.
83. Mahomed K, Williams MA, Woelk GB, Mudzamiri S, Madzime S, King IB, Bankson DD. Leukocyte selenium, zinc, and copper concentrations in preeclamptic and normotensive pregnant women. *Biol Trace Elem Res* 2000; 75(1-3): 107-18.
84. Hunt IF, Murphy NJ, Cleaver AE, Faraji B, Swendseid ME, Coulson AH, Clark VA, Browdy BL, Cabalum T, Smith JC, Jr. Zinc supplementation during pregnancy: effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *Am J Clin Nutr* 1984; 40(3): 508-21.

85. Mahomed K, James DK, Golding J, McCabe R. Zinc supplementation during pregnancy: a double blind randomised controlled trial. *Bmj* 1989; 299(6703): 826-30.
86. Sibai BM, Villar MA, Bray E. Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial. *Am J Obstet Gynecol* 1989; 161(1): 115-9.
87. Spatling L, Spatling G. Magnesium supplementation in pregnancy. A double-blind study. *Br J Obstet Gynaecol* 1988; 95(2): 120-5.
88. Steegers EA, Eskes TK, Jongsma HW, Hein PR. Dietary sodium restriction during pregnancy; a historical review. *Eur J Obstet Gynecol Reprod Biol* 1991; 40(2): 83-90.
89. Knuist M, Bonsel GJ, Zondervan HA, Treffers PE. Low sodium diet and pregnancy-induced hypertension: a multi-centre randomised controlled trial. *Br J Obstet Gynaecol* 1998; 105(4): 430-4.
90. Steegers EA, Van Lakwijk HP, Jongsma HW, Fast JH, De Boo T, Eskes TK, Hein PR. (Patho)physiological implications of chronic dietary sodium restriction during pregnancy; a longitudinal prospective randomized study. *Br J Obstet Gynaecol* 1991; 98(10): 980-7.
91. Bodnar LM, Tang G, Ness RB, Harger G, Roberts JM. Periconceptional multivitamin use reduces the risk of preeclampsia. *Am J Epidemiol* 2006; 164(5): 470-7.
92. Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Risk of gestational hypertension in relation to folic acid supplementation during pregnancy. *Am J Epidemiol* 2002; 156(9): 806-12.
93. Merchant AT, Msamanga G, Villamor E, Saathoff E, O'Brien M, Hertzmark E, Hunter DJ, Fawzi WW. Multivitamin supplementation of HIV-positive women during pregnancy reduces hypertension. *J Nutr* 2005; 135(7): 1776-81.
94. Roberts JM, Balk JL, Bodnar LM, Belizan JM, Bergel E, Martinez A. Nutrient involvement in preeclampsia. *J Nutr* 2003; 133(5): 1684S-1692S.
95. Bodnar LM, Catov JM, Klebanoff MA, Ness RB, Roberts JM. Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. *Epidemiology* 2007; 18(2): 234-9.
96. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. *Ann Epidemiol* 2005; 15(7): 475-82.
97. Eskenazi B, Fenster L, Sidney S. A multivariate analysis of risk factors for preeclampsia. *JAMA* 1991; 266(2): 237-41.
98. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiol* 2003; 14: 368-374.
99. Sibai BM, Ewell M, Levine RJ, Klebanoff MA, Esterlitz J, Catalano PM, Goldenberg RL, Joffe G. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *Am J Obstet Gynecol* 1997; 177(5): 1003-10.
100. Galan P, Viteri FE, Bertrais S, Czernichow S, Faure H, Arnaud J, Ruffieux D, Chenal S, Arnault N, Favier A, Roussel AM, Herberg S. Serum concentrations of beta-carotene, vitamins C and E, zinc and selenium are influenced by sex, age, diet, smoking status, alcohol consumption and corpulence in a general French adult population. *Eur J Clin Nutr* 2005; 59(10): 1181-90.

101. Wallstrom P, Wirfalt E, Lahmann PH, Gullberg B, Janzon L, Berglund G. Serum concentrations of beta-carotene and alpha-tocopherol are associated with diet, smoking, and general and central adiposity. *Am J Clin Nutr* 2001; 73(4): 777-85.
102. Apovian CM. Sugar-sweetened soft drinks, obesity, and type 2 diabetes.[comment]. *JAMA* 2004; 292(8): 978-9.
103. Marcoux S, Brisson J, Fabia J. The effect of leisure time physical activity on the risk of pre-eclampsia and gestational hypertension. *J Epidemiol Community Health* 1989; 43(2): 147-52.
104. Sorensen TK, Williams MA, Lee IM, Dashow EE, Thompson ML, Luthy DA. Recreational physical activity during pregnancy and risk of preeclampsia. *Hypertension* 2003; 41(6): 1273-80.
105. Saftlas AF, Logsden-Sackett N, Wang W, Woolson R, Bracken MB. Work, leisure-time physical activity, and risk of preeclampsia and gestational hypertension. *Am J Epidemiol* 2004; 160(8): 758-65.
106. Rudra CB, Williams MA, Lee IM, Miller RS, Sorensen TK. Perceived exertion during prepregnancy physical activity and preeclampsia risk. *Med Sci Sports Exerc* 2005; 37(11): 1836-41.
107. Leveno KJ, Cunningham G. Management of preeclampsia. In: *Chesley's Hypertensive Disorders in Pregnancy*. Lindheimer M, Roberts JM, Cunningham G, ed. Stamford, CT:Appleton & Lange 1999: 543-580.
108. U.S. Department of Health and Human Services and the U.S Department of Agriculture, *Dietary Guidelines for Americans 2005*. <http://www.health.gov/dietaryguidelines/dga2005/document/>. 2005.
109. Institute of Medicine, *Nutrition during Pregnancy and Lactation: an Implementation Guide*. 1992, Washington, D.C.: National Academy Press.
110. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. [See comment]. *Lancet* 2006; 368(9542): 1164-70.
111. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity.[see comment][erratum appears in Am J Clin Nutr. 2004 Oct;80(4):1090]. *American Journal of Clinical Nutrition* 2004; 79(4): 537-43.
112. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome.[see comment]. *American Journal of Clinical Nutrition* 2002; 76(5): 911-22.
113. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH, Vitamins in Pre-eclampsia Trial C. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial.[see comment]. *Lancet* 2006; 367(9517): 1145-54.
114. Villar J, Belizan JM. Same nutrient, different hypotheses: disparities in trials of calcium supplementation during pregnancy. *American Journal of Clinical Nutrition* 2000; 71(5): 1375S-1379S.
115. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG, Karanja N, Lin PH, Group DA-SCR. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *New England Journal of Medicine*. 2001; 344(1): 3-10.

116. Levine RJ, Hauth JC, Curet LB, Sibai BM, Catalano PM, Morris CD, DerSimonian R, Esterlitz JR, Raymond EG, Bild DE, Clemens JD, Cutler JA. Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997; 337(2): 69-76.
117. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation* 2006; 113(4): 499-506.
118. Conde-Agudelo A, Althabe F, Belizan JM, Kafury-Goeta AC. Cigarette smoking during pregnancy and risk of preeclampsia: a systematic review. *Am J Obstet Gynecol* 1999; 181(4): 1026-35.
119. Cnattingius S, Mills JL, Yuen J, Eriksson O, Ros HS. The paradoxical effect of smoking in preeclamptic pregnancies: Smoking reduces the incidence but increases the rates of perinatal mortality, abruptio placentae, and intrauterine growth restriction. *American Journal of Obstetrics and Gynecology* 1997; 177(1): 156-161.
120. Castles A, Adams EK, Melvin CL, Kelsch C, Boulton ML. Effects of smoking during pregnancy. Five meta-analyses. *American Journal of Preventive Medicine* 1999; 16(3): 208-15.
121. Isaksen CV, Austgulen R, Chedwick L, Romundstad P, Vatten L, Craven C. Maternal smoking, intrauterine growth restriction, and placental apoptosis. *Pediatric and Developmental Pathology* 2004; 7(5): 433-442.
122. Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? *J Hypertens* 1999; 17(9): 1307-15.
123. Forest JC, Girouard J, Masse J, Moutquin JM, Kharfi A, Ness RB, Roberts JM, Giguere Y. Early occurrence of metabolic syndrome after hypertension in pregnancy. *Obstetrics & Gynecology* 2005; 105(6): 1373-80.
124. Owen CG, Whincup PH, Gilg JA, Cook DG. Effect of breast feeding in infancy on blood pressure in later life: systematic review and meta-analysis. *BMJ* 2003; 327(7425): 1189-95.