International Journal of Gynecology and Obstetrics 81 (2003) 257–262

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Article

Effect of lycopene on pre-eclampsia and intra-uterine growth retardation in primigravidas

J.B. Sharma*, Ashok Kumar, A. Kumar, M. Malhotra, R. Arora, S. Prasad, S. Batra

Department of Obstetrics and Gynecology, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India

Received 10 October 2002; received in revised form 6 January 2003; accepted 15 January 2003

Abstract

Objectives: To observe the effect of the antioxidant lycopene on the occurrence of pre-eclampsia and intrauterine growth retardation in primigravida women. *Methods:* A total of 251 primigravida women were enrolled in this prospective, randomized controlled study in the second trimester. A total of 116 women were given oral lycopene (Group I) in a dose of 2 mg twice daily while 135 women were given a placebo (Group II) in the same dose until delivery. The criteria for recruitment included gestational age of 16–20 weeks, singleton pregnancy, absence of any medical complication and willingness on the part of the women to participate in the study. The women were followed-up until delivery for development of pre-eclampsia, mode of delivery and fetal outcome. *Results:* The two groups were comparable in their maternal characteristics. Pre-eclampsia developed in significantly less women in the lycopene group than in the placebo group (8.6% vs. 17.7%, $P=0.043$ by chi-square test). Mean diastolic blood pressure was significantly higher in the placebo group (92.2 ± 5.98 mmHg vs. 86.7 ± 3.80 mmHg, $P=0.012$). Mean fetal weight was significantly higher in the lycopene group (2751.17 ± 315.76 g vs. 2657 ± 444.30 g, $P=0.049$). The incidence of intrauterine growth retardation was significantly lower in the lycopene group than in the placebo group (12% vs. 23.7%, $P=0.033$). *Conclusions:* The results of the present study suggest that the antioxidant lycopene reduces the development of pre-eclampsia and intrauterine growth retardation in primigravida women.

Keywords: Antioxidant; Pre-eclampsia; Lycopene; Intrauterine growth retardation; Pregnancy

1. Introduction

Pre-eclampsia is a human pregnancy specific disorder that adversely affects the mother by vascular dysfunction and the fetus by intrauterine growth restriction [1]. Using the definition of the International Society for the Study of Hypertension in Pregnancy (ISSHP), non-proteinuric pregnancy induced hypertension (PIH) may be estimated to develop in 8–10% of nulliparous women; pre-eclampsia in 2–3% and eclampsia in approximately five to six per 10 000 pregnancies beyond 20 weeks' duration [2]. The main risk of non-proteinuric PIH is the later development into proteinuric pre-eclampsia and eclampsia which are one of the

*Corresponding author. AI/61, Azad Apartments, Sri Aurobindo Marg, New Delhi-110016, India. Tel.: +91-11-2696-8871; fax: +91-11-2686-6961.

E-mail address: jbsharma@eth.net (J.B. Sharma).

0020-7292/03/$30.00
PII: S0020-7292(03)00040-7

leading contributors to maternal mortality, with cerebral hemorrhage as the most primary cause of death [3,4]. Hypertensive disorders of pregnancy are also a major cause of perinatal mortality in particular due to abruptio placentae, fetal growth restriction and iatrogenic preterm delivery [5]. The major cause of fetal compromise is reduced uteroplacental perfusion.

Pre-eclampsia remains a disease of theories and no single hypothesis can explain the etiology. It is associated with widespread vasospasm, pathological lesions within multiple organ systems including the uteroplacental vascular bed and increased platelet activation with platelet consumption and subsequent activation of the coagulating system in the microvascular circulation [6]. There is impairment of endothelial cell function in pre-eclampsia with characteristic morphologic lesions such as glomerular endotheliosis, imbalance between vasodilator and vasoconstrictor eicosanoid synthesis, resulting in the general increase in sensitivity to vasopressors with ultrastructural changes in placental bed and uterine vessels. There is imbalance between lipid peroxidation and antioxidant defenses leading on to endothelial dysfunction and free radical mediated endothelial cell injury in pre-eclampsia [7–9]. There is some evidence that protective antioxidant systems are deficient in pre-eclampsia as lower placental tissue and maternal serum carotenoid levels such as β-carotene, lycopene, and canthaxanthin have been observed in pre-eclampsia [10–12]. However, Schiff et al. could not find any evidence of low vitamin E concentration in pre-eclamptic patients [13]. Only one study could find possible beneficial effects of supplementation with vitamin C and E in the prevention of pre-eclampsia [14]. No other study has been done to our knowledge using the antioxidant lycopene in its prevention.

The purpose of this study was to see the effect of lycopene, an antioxidant, on prevention of pre-eclampsia and intrauterine growth retardation (IUGR) in primigravida women.

2. Materials and methods

A total of 251 women attending the antenatal clinics of Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi were recruited. Inclusion criteria were primigravidas, with gestation between 16 and 20 weeks with absence of any medical complication such as renal disease, primary hypertension, cardiovascular disease, diabetes, or connective tissue disease. Power analysis was performed to decide the total number of women in each category of treatment. Considering the incidence of pre-eclampsia to be 7–10% in primigravidas, and taking 5% as error, a sample size of approximately 124 women in each group was calculated.

Group I women were given 2 mg lycopene twice daily, as LycoRed™ soft gelatin capsules, manufactured by Jagsonpal Pharmaceuticals Ltd., New Delhi, India, under license from LycoRed Natural Products Industries Ltd., BeerSheva, Israel, makers of natural lycopene, LYC-O-MATO™. Group II were given similar looking placebo tablets in the same dosage. Written informed consent was taken from all the women for inclusion into the study. Randomization was done using computer generated numbers. The departmental ethical committee cleared the study. Patients were given either the drug or placebo with a dose of one soft gel twice a day until delivery. Triplicate copies of stickers with the same code number were pasted on the patient's OPD card, proforma with patient's details and container carrying the drug. This was done to later identify whether the patient was on the drug or the placebo and also to give the patient the same capsule as they had taken in the previous month. The women were properly counseled to take the medicine regularly, and were seen by the same doctor on each visit to ascertain the compliance. The pill count was done on each visit. Data of only those women who took the medications regularly and completed the study were taken for analysis. Dating of the pregnancy was done using definite menstrual history and ultrasound scan done in the first trimester. Lubchenco growth curves were used from the computer in the ultrasound machine in the IUGR cases. IUGR term was used for a fetus whose weight was below the 10th percentile for its gestational age [15]. The treatment with the drug or placebo was continued until delivery. Thus the women took the treatment for 20–24 weeks (140–168 days).

Table 1
Characteristics of women

S. no.	Characteristic	Group I ($n=116$)	Group II ($n=135$)	*P*-value	Significance
1.	Mean maternal age in years	22.56	21.77	>0.05	NS
2.	Mean education (in years)	8.57	9.28	>0.05	NS
3.	Religion				
	Hindu	76 (65.6%)	93 (68.8%)	>0.05	NS
	Muslim	40 (34.4%)	42 (31.2%)		
4.	Mean gestational age at start of study (weeks)	21.34 ± 4.94	21.99 ± 5.14	>0.05	NS

During enrolment the blood pressure (BP) and proteinuria were recorded. All the doctors who participated in the trial were trained to take blood pressure in a similar way to maximize reproducibility and for better accuracy. The blood pressure was always taken by one of the doctors of the trial in the right arm supine position and the 5th Korotkoff sound was taken for diastolic BP. They were given dates for their next visit, 1 month later. On subsequent visits the BP and urine analysis for proteinuria were taken again and patient given the next month's course of drug or placebo as per the coded number on the patient's proforma. All the patients were followed up for development of pre-eclampsia. Pre-eclampsia was defined as described by International Society for Study of Hypertension in Pregnancy. Hypertension was defined as one in which diastolic blood pressure (DBP) reading was >110 mmHg or two consecutive diastolic BP ≥ 90 mmHg ≥ 4 h apart, or an increase in 20 mmHg in DBP; or systolic blood pressure (SBP) >140 mmHg or a 30 mmHg increase in SBP in patients enrolled as normotensive. Significant proteinuria was >300 mg protein in a 24-h urine collection or $1+$ dipstick on two consecutive occasions 4 h apart. Although the protein/creatinine ratio is a better indicator of significant proteinuria than estimation of proteins alone in urine, only quantitative estimation of proteinuria was made in the present study as the facilities of protein/creatinine ratio were not available in our laboratory. Although it would have been important to determine the antioxidant content of the diet of the women in such a study, diet analysis was not performed due to lack of facilities. As the two groups were similar in all aspects, it is presumed that the antioxidant contents of the diet in both the groups were probably similar.

In the labor room, the details of patients with stickers on OPD cards were recorded, such as period of gestation during delivery, BP during delivery, mode of delivery, fetal weight, etc. These data were collected and recorded. The final data were subjected to statistical analysis.

2.1. Statistical analysis

Data were statistically analyzed with one-way analysis of variance to detect significant differences between means in the drug and placebo groups. The unpaired *t*-test was used to detect significance between the two groups for parametric values. Chi-square tests and symmetric measures were done. A value of $P<0.05$ was considered statistically significant. As all the predisposing factors and high risk factors were already excluded at enrolment, linear regression to adjust them was not performed.

3. Results

The characteristics of the women in the two groups are shown in Table 1. There was no significant difference in the mean age, socio-economic status, religion and mean gestational age at booking in the two groups.

Table 2 shows the maternal and fetal outcome in the two groups. There was significantly lower incidence of pre-eclampsia and IUGR and significantly higher fetal weight and gestation in the lycopene group than in the placebo group. Overall there was 51.4% reduction in pre-eclampsia and

Table 2
Effect of lycopene and placebo on maternal fetal outcome

S. no.	Characteristic	Group I ($n=116$)	Group II ($n=135$)	*P*-value	Significance
1.	Pre-eclampsia	10 (8.6%)	24 (17.7%)	0.043	Significant
2.	Eclampsia	0	1 (0.74%)	<0.05	Significant
3.	Mean diastolic blood pressure (mmHg)	86.7 ± 3.80	92.2 ± 5.98	0.012	Significant
4.	Intrauterine growth retardation (IUGR)	14 (12%)	32 (23.7%)	0.033	Significant
5.	Mean fetal weight (g)	2751.17 ± 315.76	2657.26 ± 444.30	0.049	Significant
6.	Mean gestation (weeks)	37.72 ± 1.61	36.56 ± 2.2	<0.05	Significant

49.3% reduction in IUGR with the antioxidant lycopene. Mean diastolic blood pressure was significantly lower (86.7 ± 3.80 mmHg) in the lycopene group than in the placebo group (92.2 ± 5.8 mmHg) ($P=0.012$). There was one case of eclampsia in the control group but none in the lycopene group, but the number was too small for any statistical significance.

4. Discussion

Vascular endothelial damage is known to play a role in the pathophysiologic mechanisms of pre-eclampsia [7–9,14]. It has been suggested that free radical mediated lipid peroxidation may be involved in endothelial damage seen in pre-eclampsia [7–11]. Excess free radical disturbances are typically accompanied by increased utilization of antioxidants resulting in a decrease in their concentration [8–14].

Carotenoids are natural pigments synthesized by plants and micro-organisms to serve as light ablating pigments during photosynthesis and protection of cells against photosensitization [16]. More than 600 carotenoids have been characterized sharing a common polyisoprenoid structure and a series of centrally located conjugated double bonds [16]. The major classes of dietary carotenoids are beta-carotene, lycopene and the more polar oxycarotenoids or xanthophils such as lutein, beta-cryptoxanthin and canthaxanthin. Lycopene is an acyclic carotenoid with 11 linearly arranged conjugated double bonds and found in relatively few foods. Lycopene lacks the beta-ionone ring structure and is therefore devoid of provitamin A activity. It is a prominent carotenoid in human plasma and tissue making more than 50% of the total carotenoid content of the human body [16,17]. Dietary lycopene is derived only from a limited list of foods like tomatoes, guava and watermelon in contrast to other major carotenoids. Lycopene is a prominent carotenoid in the adrenals, testes, liver and prostate [18]. Many of the putative biological effects and health benefits of lycopene and other carotenoids are hypothesized to occur via protection against oxidative damage [17]. There is some evidence that lack of carotenoids especially lycopene has been found to be associated with cancers of the digestive tract, cervical intra-epithelial neoplasms, breast cancer, skin cancer, bladder cancer, prostate cancer and cardiovascular diseases [19–25].

Many studies confirm that level of vitamin C and E which are potent antioxidants are reduced in pregnancies complicated by pre-eclampsia and the reduction appears to be higher in severe pre-eclampsia and eclampsia [8,26,27]. Palan et al. [12] found significantly lower levels of β-carotene, lycopene and canthaxanthin in maternal serum and placentas of pre-eclamptic women than in normotensive women. They suggested that a dietary antioxidant influence might have an effect on the pathophysiology of pre-eclampsia. A potential role for the antioxidant micronutrients like carotenoids, vitamin C and vitamin E in modifying many medical conditions has stimulated intense research efforts, increased interest in micronutrient supplements and heightened consumer interest in these compounds [27]. This is especially important in view of failure of other modalities like low dose

aspirin, magnesium, zinc or fish oil supplementation, calcium supplementation and various antihypertensive drugs along with diuretics to prevent pre-eclampsia [28]. In view of these disappointments and scientific evidence and safety in their favor, the role of micronutrients and antioxidants in preventing pre-eclampsia is promising.

In fact a randomized controlled trial investigated the effect of supplementation with vitamin C and E on plasma markers of vascular endothelial activation (plasminogen activator inhibitors -1, PAI-1) and placental insufficiency (PAI-2) and the occurrence of pre-eclampsia [14]. In the intention to treat cohort pre-eclampsia occurred in 17% women in placebo group and 8% in vitamin group thereby suggesting that supplementation with vitamin C and E may be beneficial in the prevention of pre-eclampsia in women at increased risk of disease [14]. In another recent study, the same authors have observed that use of vitamin C and E was helpful in improving the biochemical indicators of pre-eclampsia in women who are at risk [29].

In the present study lycopene, a carotenoid with no pro-vitamin A activity and with the highest number of double bonds, which are responsible for its scavenging action, was used in primigravida women. Pre-eclampsia occurred in 17.7% women in placebo group and in 8.6% women in lycopene group with an overall reduction of 51.4%. Even IUGR was observed in 12% women on lycopene in contrast to 23.7% in the placebo group, a 49.3% reduction. Another recent study showed antioxidant vitamins C, E and β-carotene supplementation reduced the oxidative stress at delivery in mothers and probably in their neonates also [30].

Lycopene is a carotenoid micronutrient which is safe to consume and its levels are highly reduced in pre-eclampsia and eclampsia [12]. The results of the present study are very encouraging and lycopene has been found to be very effective in significantly reducing the occurrence of pre-eclampsia and IUGR. This is the first study of its kind to the best of our knowledge, which has used lycopene in the prevention of pre-eclampsia. Large multi-centric studies are recommended to confirm the findings of the present study, which if proved will be a significant landmark in the prevention of pre-eclampsia.

References

[1] Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200–1204.

[2] Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988;158:892–898.

[3] Duley L. Material mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol 1992;94:547–553.

[4] Department of Health: Welsh Office: Scottish Home and Health Department: Department of Health and Social Services, Northern Ireland. Report on confidential enquiries into maternal deaths in the United Kingdom, 1978–1988. London: HM Stationery Office, 1994. p. 22–33.

[5] Wallenburg HCS, Visser W. Pregnancy induced hypertensive disorders. Curr Opin Obstet Gynecol 1994;6:14–29.

[6] Sibai BM. Preeclampsia–eclampsia. Curr Prob Obstet Gynecol Fertil 1990;13:1–45.

[7] Hubel CA, Roberts JM, Taylor RN, Musci TJ, Rogers GM, McLaughhn MK. Lipid peroxidation in pregnancy: new perspectives on preeclampsia. Am J Obstet Gynecol 1989;161:1025–1034.

[8] Mikhail MS, Anyaegbunam A, Garfinkel D, Palan PR, Basu J, Romney SL. Preeclampsia and antioxidant nutrients: decreased plasma levels of reduced ascorbic acid, α-tocopherol and β-carotene in women with preeclampsia. Am J Obstet Gynecol 1994;171:150–157.

[9] Wisdom SJ, Wilson R, McKillop JH, Waller JJ. Antioxidant systems in normal pregnancy and in pregnancy induced hypertension. Am J Obstet Gynecol 1991;165:1701–1704.

[10] Uotila JT, Tumala RJ, Aarmo TM, Pyykkö KA, Ahotupa MO. Findings on lipid peroxidation and antioxidant function in hypertensive complications of pregnancy. Br J Obstet Gynaecol 1993;100:270–276.

[11] Sagol S, Özkinay E, Özsevers S. Impaired antioxidant activity in women with pre-eclampsia. Int J Gynecol Obstet 1999;64:121–127.

[12] Palan PR, Mikhail MS, Romney SL. Placental and serum levels of carotenoids in pre-eclampsia. Obstet Gynecol 2001;98:459–462.

[13] Schiff E, Friedman SA, Stamper M, Kao L, Barren PH, Sibai BM. Dietary consumption and plasma concentrations of vitamin E in pregnancies complicated by preeclampsia. Am J Obstet Gynecol 1996;175(4):1024–1028.

[14] Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence

of pre-eclampsia in women at increased risk; a randomised trial. Lancet 1999;354(9181):810–816.
[15] Battalgia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr 1967;71:159.
[16] Clinton SK. Lycopene: chemistry, biology, and implications for human health and disease. Nutr Rev 1998;56(2):35–51.
[17] Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch Biochem Biophys 1989;274(2):532–538.
[18] Kaplan LA, Lau JM, Stein EA. Carotenoid composition, concentrations and relationships in various human organs. Clin Physiol Biochem 1990;8:1–10.
[19] Tsugane S, Tsuda M, Gey F, Watanabe S. Cross-sectional study with multiple measurements of biological markers for assessing stomach cancer risks at the population level. Environ Health Perspect 1992;98:207–210.
[20] VanEewyck J, Davis FG, Bowen PE. Dietary and serum carotenoids and cervical intraepithelial neoplasia. Int J Cancer 1991;48:34–38.
[21] Garland M, Willett WC, Manson JE, Hunter DJ. Antioxidant micronutrients and breast cancer. J Am Coll Nutr 1993;12:400–411.
[22] Ribayo-Mercado JD, Garmyn M, Gilchrest BA, Russell RM. Skin lycopene is destroyed preferentially over carotene during ultraviolet irradiation in humans. J Nutr 1995;125:1854–1859.
[23] Helzlsouer KJ, Constock GW, Morris JS. Selenium, lycopene, α-tocopherol, β-carotene, retinol, and subsequent bladder cancer. Cancer Res 1989;49:6144–6148.
[24] Giovannucci EL, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relationship to risk of prostate cancer. J Natl Cancer Inst 1995;87:1767–1776.
[25] Frei B. Cardiovascular disease and nutrient antioxidants: role of low-density lipoprotein oxidation. Crit Rev Food Sci Nutr 1995;351:83–98.
[26] Kharb S. Vitamin E and C in preeclampsia. Eur J Obstet Gynecol Reprod Biol 2000;93:37–39.
[27] Rock CL, Jacob RA, Bowen PE. Update on the biological characteristics of the antioxidant micronutrients: vitamin C, vitamin E and the carotenoids. J Am Diet Assoc 1996;96:693–702.
[28] Sibai BM. Prevention of preeclampsia: a big disappointment. Am J Obstet Gynecol 1998;179:1275–1278.
[29] Chappell LC, Seed PT, Kelly FJ, Briley A, Hunt BJ, Chamock-Jones DS, et al. Vitamin C and E supplementation in women at risk of preeclampsia is associated with changes in indices of oxidative stress and placental function. Am J Obstet Gynecol 2002;187(3):777–784.
[30] Bolisetty S, Naidoo D, Lui K, Koh TH, Watson D, Whitehall J. Antenatal supplementation of antioxidant vitamins to reduce oxidative stress at delivery—a pilot study. Early Human Dev 2002;67(1/2):47–53.