Short Communication

Efficacy of Micronutrient Supplementation During Antenatal Period: An Open Label Randomized Control Trial

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An open label randomized control trial was conducted to evaluate the efficacy of micronutrients among pregnant women and assessing the antenatal and fetal complications associated with the same. The participants were randomized into intervention and control groups. The intervention group was administered with micronutrient supplementation. Demographic characteristics were captured following which analysis was done. The distribution of the demographic characteristics was assessed using independent t test and Chi square test. Multivariate analysis was performed to find the efficacy of micronutrients in terms of gestational week, body mass index, blood pressure, maternal body weight and birth weight of babies between the groups. Out of 33 subjects participated in the study, 9.09 % of the subjects delivered babies with low birth weight in treatment group, while 13.6 in control group. Patients who received 5 mo and 6 mo of micronutrients showed acceptable gestational period of 34 mo. There was a significant increase in body mass index and mid abdominal circumference in treatment group (p=0.04) in comparison to the control group. Study concluded that the addition of multiple micronutrients during gestation improves pregnancy outcomes in terms of gestational week, birth weight of babies and also body mass index, mid arm circumference and mid abdominal circumference.

Key words: Micronutrient, pregnancy, intrauterine growth retardation, supplementation, foetal complications

Micronutrients are required in small quantities due to their increased requirements at the time of pregnancy. Its deficiency is common in low income countries and it can lead to adverse outcomes on the mother and developing fetus. Poor maternal nutritional can contribute to infant mortality and morbidities such as respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis and hypoglycemia. In developing countries nearly 6-30 % of infants are born with low birth weight, nearly one-third of them are small for gestational age[1]. Multivitamin supplementation mainly includes folate, vitamin B12, vitamin B6, vitamin A, vitamin D, vitamin E and certain trace elements (zinc, iodine, copper, selenium). Population-based studies conducted in Bangladesh, Nepal and India have reported deficiencies of vitamin B12 (19-74 %), folate (0-26 %), vitamin E (50-70 %) and zinc (15-74 %) in pregnant women, while global estimates of other deficiencies are unavailable[2-5]. Micronutrients play a major role in supporting pregnancy and maintaining fetal health. Its deficiency can affect the development of embryo prior to its implantation. Insufficiency of vitamin B6, vitamin B12 and folate is associated with epigenetic changes in fetal deoxyribonucleic acid. This could increase susceptibility of the offspring to hypertension, diabetes mellitus and obesity in adulthood[6]. Based on the results of *in vitro* studies, α-tocopherols are required to maintain integrity of lipid membranes *via* antioxidants.

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Oxidative stress associated with decreased antioxidant levels can affect the vascularization of placental tissues[7]. Other micronutrients support the hemodynamic changes in pregnancy pertaining to systems such as renal, cardiovascular and gastrointestinal. There has been several reports of miscarriage associated with deficiencies of trace elements such as selenium, zinc and copper[8]. The influence of micronutrients on pregnancy outcomes is not well defined. Hence, our study establishes the improvement in maternal and foetal health following micronutrient administration. This is an open label randomized control trial that was carried out at the Obstetrics and Gynecology department of a secondary care public hospital. A total of 44 pregnant women were enrolled based on the sample size calculated using PS power and sample size calculator version 3.0.14. The study was conducted for a period of 6 mo with six visits including the baseline. All materials and methods used in the study were approved by the Institutional Review Board, prior to its initiation. The study included pregnant women who were in their first or second trimester of pregnancy confirmed to have a singleton birth by ultrasonography test with an ability to provide written consent. The exclusion criteria mainly comprised of pregnant women having an existing illness of severity (hypertension, renal disease, heart disease, diabetes mellitus, urinary tract infection, tuberculosis, psychiatric illness) that could compromise the pregnancy outcomes. Pregnant women suspected to hypersensitivity or contraindications to any of the ingredients of the study medication were also not included. Participants who were unable to follow the study procedure and suspected non-compliance were excluded from analysis. The study participants were randomized into the experimental and control group with a 1:1 allocation ratio using random allocation software. The micronutrient formulation used as the intervention were the Fixed Dose Combinations (FDC) constituted of ascorbic acid-150 mg, calcium pantothenate-50 mg, folic acid-1.5 mg, niacinamide-100 mg, pyridoxine HCl-3 mg, riboflavin-10 mg, thiamine mononitrate-10 mg, Vitamin B12-15 mcg, zinc sulphate monohydrate-4 mg and biotin-100 mcg. Batch no-TOW2005AL. The iron-folic acid was also the FDC used in the study that contained dried ferrous sulphate-333 mg, folic acid-0.5 mg and calcium lactate-150 mg. Batch no-BP1209. Manufacturer is Eurokem laboratories pvt ltd. Both these FDC formulations were generic formulations supplied to the Government hospitals in the state of Tamil Nadu, the investigators had no control over the products supplied to the study participants. However, the study was conducted in a real time uncontrolled conditions of the patients' living styles. Prenatal depression was assessed using Edinburgh Depression Scale, which is a 10 item questionnaire specifically designed for screening depression among pregnant women. A score of 13 was considered as the cut-off to rule out the possibility of depression. Prenatal anxiety was assessed using Spielbergers state anxiety inventory that consists of 20 questions that might influence anxiety levels. Data was entered into a specially designed data collection form that captured information such as gestational age, body weight, anthropometric data, ultrasonography report and evidence for any comorbid conditions as per exclusion criteria. A written consent was obtained from the eligible participants who met the study criteria. They were randomized into either of the 2 groups using a computerized randomization technique at baseline. Follow ups were done after every 30 d until the date of delivery, during which participant's weight and physical status was assessed. The intervention group was administered with micronutrients along with iron-folic acid while the control group received only iron-folic acid supplements. They were counselled adequately and asked to enter in the compliance card given to them for assessing adherence following each administration. The birth weights of the babies were recorded and the effects of multiple micronutrient supplements were compared with that of iron-folic acid. The data was analyzed using Statistical Package for the Social Sciences software version-17.0 and Epi Info-2002. Descriptive statistics was performed for the demographic characteristics of the participants. Continuous variables were expressed as mean±standard deviation and categorical variables as percentages. Independent t test was used to analyze continuous variables and Chi-square test for categorical variables. Multivariate analysis was performed to find the efficacy of micronutrients in terms gestational week, Body Mass Index (BMI), blood pressure, maternal body weight and birth weight of babies between the groups. The p value<0.05 was considered statistically significant. A total of

44 pregnant females met the eligibility criteria and were randomized into treatment group (n=22) and control group (n=22) using computerized randomization. Data were collected from the eligible participants and their compliance to the medications was measured following the baseline visit. As a whole, 33 subjects completed the study (18 in the treatment group and 15 in the control group). 6 pregnant women were lost to follow up, and the remaining 5 had spontaneous abortion or other medical condition resulting in fetal loss. Demographic characteristics have given in Table 1. The demographic characteristics were equally distributed in both the groups. Physical examination, vital signs and blood chemistry of 44 study participants in the treatment and control groups is shown in Table 2. This study comprised of pregnant women with a mean gestation age of 15.8±3.7. The age of the participants was 22.7±3.02 y in the treatment group and 24±4.4 y in the control group. The participants in the study had a normal BMI of 21.7±3.8 kg/m^2. There was a statistically significant difference in the distribution of education and employment status in both the groups. 90 % of the participants were on daily wages with a monthly income of 1000-2000 INR (66.6 % in the treatment group and 80 % in the control group). The hemoglobin levels were equally distributed between the groups. The distribution of compliance (0.96±0.05 *vs*. 0.98±0.04) and birth weight (2.7±0.38 *vs*. 2.74±0.28) of infants were similar in both the groups. Monthly variation in weeks of gestation, BMI, blood pressure, Mid Arm Circumference (MAC) and Mid Abdominal Circumference (MADC) between both the groups were compared using multivariate analysis. There was no significant difference (p>0.05) in BMI between test and control group subjects who were in 4 mo of treatment period. However, it was significantly improved following 5 mo of treatment with a p value of 0.04. Though the BMI improved with 6 mo of treatment, it was equally distributed between both the groups. Participants who received micronutrients for 4 mo (n=2) did not have an acceptable gestational age (30 mo) and delivered preterm (n=2). Whereas on 5 mo (n=15) and 6 mo (n=12) of micronutrients an acceptable gestational period of 34 w was seen even though they delivered preterm. This effect did not differ in the treatment and control groups. Almost 16 antenatal complications were noted in the subjects who were participated in the study. The patients reported these complications during the visits and were treated for the complications. The most commonly noted complications were fever and urinary tract infection. None of the patients required any emergency treatment or hospital admissions due to these complications but were managed. The antenatal complications are illustrated in Table 3. Out of 44 subjects that participated in the study, 3 (13.6 %) subjects delivered babies with low birth weight in treatment group, while 2 (9.09 %) in control group. Almost 9.09 % intrauterine death was observed in the control group (n=5). The treatment group reported no incidence of death. With regard to birth weight of neonates there was no significant difference (p>0.05) between both the groups. The average percentage of compliance among treatment and control groups were found to be 96 % and 98 %, respectively. Compliance was more in control group than test group but was not significantly different (p=0.18). Prenatal women admitted for delivery were assessed for depression and anxiety. It was observed that 19 (37.5 %) of the subjects admitted in the antenatal ward showed a risk of depression. The average score of anxiety in prenatal women (n=8) was observed to be 53.7 which was observed among 50 % of the subjects. Patients who received micronutrients for 5-6 mo showed an acceptable gestational period of 34 mo. Our results suggest that the gestational week was increased with micronutrients which are also similar to the study findings of Zeng *et al*.[9], where there was a significant increase in the mean duration of gestation in both the iron-folic acid and multiple micronutrients compared with folic acid[9]. In 5 mo of treatment with micronutrients the participants gave birth to equal number of full term and preterm babies. However, with 6 mo of treatment the incidence of preterm births was significantly reduced. A similar trend in lower rate of preterm delivery was observed by Grivell *et al*.[10] and Roberfroid *et al*.[11] among zinc-supplemented women of normal bodyweight. Spiegelman *et al*.[12] observed that low BMI patients are at an increased risk for a number of adverse pregnancy outcomes, including preterm birth and intra uterine growth retardation. Women with a low BMI were more likely to have an infant that was smaller or of lower birth weight[13]. In the current study, BMI in the treatment group was not

increased from baseline and only one subject gave birth to infant with low birth weight. Our study reports an insignificant difference ($p>0.05$) in birth weight between both the groups. Castillo-Duran *et al.*[14], Umeta *et al*.[15] and Lira *et al*.[16] revealed that the treatment with micronutrients was not influenced by birth weight. Similarly, Ramakrishnan *et al*.[17] had observed that there was no difference in birth weight or gestation duration for the group receiving micronutrients. There was no intrauterine death observed in the treatment group, however 5 deaths were noted in women received only iron and folic acid tablets, which was similar to another study by Shankar *et al*.[18] which suggested that maternal micronutrient supplementation reduced early infant mortality. Women receiving only iron-folic acid gave birth to infant with low birth weight in 5 mo treatment, while no low birth weight was noted in treatment group. The treatment effect observed in our study is consistent with the results of other studies that used UNIMMAP or a similar supplement[19]. Wiley *et al*.[20], Grivell *et al*.[21] and Oakley *et al*.[22] showed in their studies that antenatal interventions or support during pregnancy could increase the birth weight and minimize adverse pregnancy outcomes. Hence it is well established that control of antenatal complications in socio-economically poor population and support during pregnancy is a major component in preventing adverse pregnancy outcomes. Prenatal mental stress is associated with adverse outcomes such as developmental delays among infants. Studies suggest that high maternal anxiety levels during late pregnancy were associated with lower mental developmental scores at the age of 2 y[23]. The study findings suggest that in order to prevent complications due to maternal anxiety and depression, supportive care need to be given to females during late pregnancy period. In this study, randomization favoured equal distribution of prognostic factors between the groups thereby minimizing the effect of confounders on the outcome. The other strengths of this study include the presence of a comparator that establishes superiority of the intervention, the participants were adherent to the study medications, antenatal complications and adverse outcomes on the foetus were assessed. Further, the study was conducted in a real time condition without controlling the study participant's life style and habits and thus the outcomes are reflective of the real-life situation rather than a controlled study conditions. However, the limited sample size, short duration of the study treatment and the generic formulations of the supplements supplied to the Government hospitals and thus no control over the study supplements for the investigators. Thus, the types of food and their impact on the bioavailability of the micronutrients could not be studied were the major limitations of the present study. The influence of maternal mental concerns on the infant health could not be assessed. The findings of this open-label randomized control study conducted among pregnant women suggest that addition of multiple micronutrients during gestation improves pregnancy outcomes in terms of gestational week, birth weight of babies and also BMI, MAC and MADC. Patient adherence to various supplements like iron, folic acid and micronutrients during gestation is an essential factor for achieving better pregnancy outcomes. Prescribing micronutrients containing trace elements is more beneficial in comparison to use of iron supplements alone.

TABLE 1: PHYSICAL EXAMINATION, VITAL SIGNS AND BLOOD CHEMISTRY OF 44 STUDY PARTICIPANTS IN THE TREATMENT AND CONTROL GROUPS

Demographic characteristics	Total patient (N=44) mean±SD	Intervention group* (N=22) mean±SD	Control group** (N=22) mean±SD	95 % CI	p value
Weight (kg)	49.8±8.0	49.83±7.03	49.8±9.09	0.45,0.52	0.24
Age (y)	13.3±3.7	22.7±3.02	24±4.4	-0.21,0.33	0.15
BMI (kg/m^2)	21.7±3.8	21.9±2.75	21.55±4.2	-0.19,0.26	0.62
Respiratory rate (breaths/min)	23.7±5.8	25.4±6.3	22.1±5.4	-0.39,0.45	0.19
Pulse rate (beats/min)	78.8±22.5	76.6±12.6	81±9.9	-0.02,0.10	0.38

Gestation (w)	15.8±3.7	15.1±3.3	16.6±4.1	-0.44,0.50	0.50
Mid arm circumference (cm)	22.9±2.18	22.5±2.17	23.3±2.2	0.23,0.34	0.20
Mid abdominal circumference (cm)	88.8±6.6	88.2±6.6	89.5±6.7	0.62,0.79	0.29
Systolic blood pressure (mm Hg)	108.6±8.7	107.2±8.2	110±9.2	-0.97,0.12	0.45
Diastolic blood pressure (mm Hg)	70.35±5.75	69.4±4.1	71.3±7.4	-0.12,0.09	0.58
Hemoglobin (g/dl)	11.6±0.5	11.75±0.6	11.46±0.51	-0.22,0.10	0.26
Compliance	0.9±0.04	0.96±0.05	0.98±0.04	-0.92,0.14	0.87
Birth weight of infants (kg)	2.7±0.3	2.7±0.38	2.74±0.28	-0.16,0.09	0.42

Note: *Intervention group: ascorbic acid, calcium pantothenate, folic acid, niacinamide, pyridoxine HCl, riboflavin, thiamine mononitrate, Vitamin B12, zinc sulphate monohydrate and biotin; **Control group: dried ferrous sulphate, folic acid and calcium lactate; N: total number of subjects; SD: Standard deviation; p value: comparison between intervention and control groups using Independent Sample t-test

TABLE 2: DEMOGRAPHIC CHARACTERISTICS OF 44 STUDY PARTICIPANTS IN THE TREATMENT AND CONTROL GROUPS

Demographic characteristics	Total patient (N= 44) n (%)	Intervention group* (N= 22) n (%)	Control group** (N= 22) n (%)	95 % CI	p value
Education					
Illiterate	Nil	Nil	Nil	0.21,0.30	0.01
1st to 6th standard	Nil	Nil	Nil	-0.14,0.29	0.21
7th to 12th standard	30 (90.90%)	17 (99.44%)	13 (86.66%)	0.30,0.47	0.04
Above 12th	3 (9.09%)	1 (5.55%)	2 (13.3%)	0.98,0.12	0.02
Occupation					
House wife	30 (90.0%)	17 (99.4%)	13 (86.6%)	-0.12,0.24	0.09
Coolie	3 (9.09%)	1 (5.55%)	2 (13.3%)	0.18,0.29	0.03
Family income					
<1000	1 (3.03%)	Nil	1 (6.6%)	0.21,0.14	0.04
1000-2000	24 (72.7%)	12 (66.6%)	12 (80%)	0.45,0.52	0.02
2001-3000	5 (15.5%)	4 (22.2%)	1(6.6%)	0.35,0.49	0.01
3001-4000	1 (3.03%)	1 (5.5%)	0	0.14,0.27	0.01
>4000	2 (6.06%)	1 (5.5%)	1 (6.6%)	-0.98,0.12	0.20

Note: *Intervention group: Ascorbic acid, calcium pantothenate, folic acid, niacinamide, pyridoxine HCl, riboflavin, thiamine mononitrate, Vitamin B12, zinc sulphate monohydrate and biotin; **Control group: Dried ferrous sulphate, folic acid and calcium lactate; N: Total number of subjects; n: Number of subjects in a given category; %: n/Number of subjects with available results×100; SD: Standard deviation; p value: Pearson's chi-square or Fisher's exact test (for counts <5)

TABLE 3: ANTENATAL COMPLICATIONS OF STUDY PARTICIPANTS IN THE TREATMENT AND CONTROL GROUPS

Antenatal complications	Total patient (N=33) n (%)	Intervention group* (N=18) n (%)	Control group** (N=15) n (%)	p value
Fever	5 (15.1%)	3 (16.6%)	2 (13.3%)	0.24
Polyhydraminos	1(3.03%)	0	1 (6.6%)	0.15
Cephalic presentation	1(3.03%)	0	1 (6.6%)	0.62

Vomiting	2 (6.06%)	2 (11.1 %)	0	0.19
GERD	1(3.03%)	0	1 (6.6%)	0.38
IUGR	1(3.03%)	1 (5.5%)	0	0.50
UTI	4 (12.1%)	2 (11.1 %)	2 (13.3%)	0.20
Hemorrhage	1(3.03%)	0	1 (6.6%)	0.29

Note: GERD: Gastro Esophageal Reflux Disease; IUGR: Intra Uterine Growth Retardation; UTI: Urinary Tract Infection; *Intervention group: Ascorbic acid, calcium pantothenate, folic acid, niacinamide, pyridoxine HCl, riboflavin, thiamine mononitrate, Vitamin B12, zinc sulphate monohydrate and biotin; **Control group: Dried ferrous sulphate, folic acid and calcium lactate; N: Total number of subjects; n: Number of subjects in a given category and %: n/Number of subjects with available results×100

Ethical approval:

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the appropriate ethics committee. Written informed consent was obtained from all patients. The data of pregnant women used to support the findings of this study are restricted by the Institutional review board, JSS College of Pharmacy, Ooty in order to protect patient privacy. Data are available from Dr. Sabin Thomas, Assistant Professor in Pharmacy Practice, School of Pharmacy, College of Pharmacy and Nursing, University of Nizwa, Oman for researchers who meet the criteria for access to confidential data.

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Conflict of Interest:

The authors declare that they have no conflict of interest.

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