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ORIGINAL ARTICLE

# IMPACT OF LIPID-BASED NUTRITIONAL SUPPLEMENTATION IN PRIMI-GRAVIDAS AND ITS EFFECT ON MATERNAL, BIRTH AND INFANT OUTCOMES: A RANDOMIZED CONTROLLED TRIAL

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## ABSTRACT

**OBJECTIVE:** To find out the effect of Lipid based nutritional supplement (LNS) on body composition, hematological findings, maternal, birth and infant outcomes in underweight primi-gravidas.

**METHODS:** This single-blinded randomized controlled clinical trial was executed in the tertiary care hospitals of Khyber Pakhtunkhwa province, Pakistan from April 2018 to August 2019. Forty primi-gravidas recruited in the study were randomized into LNS and placebo groups. LNS group received 75 gms of high energy nutritional supplement, named "MAAMTA", on daily basis from their first antenatal visit till delivery in addition to their conventional antenatal treatment. Fasting blood samples were taken and body composition was measured at baseline visit, 16th week of gestation and post-natally. For the measurement of hematological parameters neonates cord blood was obtained. Data of 36 participants (LNS group n=19; placebo group n=17) were available for final analysis.

**RESULTS:** Majority (n=33/36; 91.7%) had normal vaginal deliveries (n=18/19 in LNS group & n=15/17 in placebo group). Frequency of Cesarean section was 1/19 (5.3%) in LNS group and 2/17 (11.8%) in placebo group. No case of abortion was reported. Mean crown heel length (CHL) was 47.11±2.747 cm in LNS group and 44.24±2.359 cm in placebo group (p=0.002). Mean fronto-occipital circumference was 35.11±1.663 cm and 32.41±7.859 cm in the LNS and placebo groups respectively (p=0.153). No difference was observed between the groups in maternal gestational weight gain per visit, prevalence of maternal anemia, maternal mortality & neonatal birth weight.

**CONCLUSION:** The prenatal use of LNS increases the CHL of the neonates of underweight primi-gravidas.

**Clinical Trial Registry Number:** ISRCTN 10088578

**KEY WORDS**: Pregnancy Outcome (MeSH); Lipid based nutritional supplements (Non-MeSH); Crown heel length (Non-MeSH); Fronto-occipital circumference (Non-MeSH); Mid upper arm circumference (Non-MeSH); Bioelectrical impedance scale (Non-MeSH). Dietary Supplements (MeSH); Body Weight (MeSH); Gravidity (MeSH); Infant, Low Birth Weight (MeSH).

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## INTRODUCTION

Pregnancy is a period of change in physiology and metabolism of a woman.[1] Energy and nutrient requirements are increased during pregnancy to meet the increased maternal metabolism, blood volume and the delivery of nutrients to the fetus.[2] More than 20 million infants with low birth weight are born every year worldwide. Among these, 3.6 million infant's deaths are of neonatal period. Maternal and child under nutrition are the causes of more than one third of child deaths.[3] According to WHO, majority of low birth weight (LBW) births occur in low and middle-income countries with regional estimates of LBW include 28% in South Asia, 13% in Sub-Saharan Africa and 9% in Latin America.[4] Globally, over 50% of the LBW occurs in South Asia, in which Pakistan and India are the major contributors.[5]

In low income countries, during pregnancy poor nutrition is associated with adverse maternal and fetal outcomes & in high income countries, over-nutrition is associated with maternal obesity and the long term derangement in the metabolic outcomes in the infants.[6] In women and children from the low and middle-income countries, poor health and development outcomes are due to micronutrient deficiencies.[7] In order to overcome the micronutrient deficiencies, multi vitamins are used by the women, although there is a lack of data on whether pre- or peri-conception supplementation with multiple micronutrients is beneficial to pregnancy outcomes.[8] In different parts of the world iron, folic acid, calcium & multiple micronutrients are used to improve maternal health and nutritional status of both the mother and fetus.[9] A relatively new strategy among the nutritional interventions is small-quantity, lipid-based nutrient supplements (LNS) provided to mothers during pregnancy and infants from six months onwards to prevent maternal and child under-nutrition plus micro-nutrient deficiencies.[10] Studies on LNS supplementation have shown promising results for small sizes in pregnant and lactating women and their children.[11] In low-income countries, LNS supplements have been designed to complement diet of the children and

**TABLE I: COMPARISON OF MORPHOLOGICAL ATTRIBUTES AMONG THE GROUPS AT DIFFERENT VISITS**

| Visits | Parameters | LNS mean±SD | Placebo mean±SD | P-value |
|---|---|---|---|---|
| 1st: | Age (years) | 18.85±2.49 | 18.47±2.60 | 0.654 |
| | Height (cm) | 154.75±3.99 | 155.06±3.64 | 0.809 |
| | Weight (kg) | 41.24±3.54 | 40.92±3.02 | 0.774 |
| | Body mass index (kg/m$^2$) | 17.21±1.22 | 17.02±1.15 | 0.634 |
| | Body fat (%) | 25.24±5.39 | 23.38±4.96 | 0.285 |
| | Hydration (%) | 51.68±5.84 | 54.09±6.32 | 0.237 |
| | Bone mass (%) | 32.97±5.17 | 33.28±6.80 | 0.875 |
| | Mid upper arm circumference (cm) | 21.29±1.41 | 20.62±1.44 | 0.170 |
| 2nd: | Weight (kg) | 47.55±5.28 | 46.32±4.31 | 0.470 |
| | Body mass index (kg/m$^2$) | 19.96±2.28 | 19.36±2.28 | 0.456 |
| | Body fat (%) | 26.88±5.37 | 24.94±4.42 | 0.266 |
| | Hydration (%) | 50.27±6.13 | 51.11±5.473 | 0.681 |
| | Bone mass (%) | 35.32±5.61 | 31.56±6.94 | 0.090 |
| | Mid upper arm circumference (cm) | 21.13±1.32 | 20.40±1.24 | 0.097 |
| 3rd: | Weight (kg) | 48.02±4.67 | 46.27±4.47 | 0.289 |
| | Body mass index (kg/m$^2$) | 20.16±2.11 | 19.35±2.37 | 0.309 |
| | Body fat (%) | 25.14±5.38 | 24.13±4.42 | 0.562 |
| | Hydration (%) | 51.04±6.15 | 53.04±6.27 | 0.357 |
| | Bone mass (%) | 32.71±5.42 | 31.65±6.64 | 0.611 |
| | Mid upper arm circumference (cm) | 21.41±1.41 | 20.77±1.30 | 0.170 |

Significant difference (*P<0.05, **P<0.01, ***P<0.001), LNS: Lipid bases nutritional supplement

pregnant women.[12] Similar products combining vegetable oil, groundnut paste, milk, sugar and micro-nutrients are being used as ready to use therapeutic foods in the management of severe acute malnutrition.[13] This study was conducted to find out the effect of LNS on body mass composition, hematological findings pregnancy and fetal outcomes in underweight primi-gravidas.

## METHODS

This study was a single blinded, randomized controlled trial (ISRCTN 10088578) carried out in the tertiary care hospitals of Khyber Pakhtunkhwa province of Pakistan from April 2018 to August 2019. Ethical approval of the study was taken from ethical review board of Khyber Medical University and the concerned hospitals (DIR/KMU-EB/EH/000453).

**Selection criteria:**

The inclusion criteria included healthy, underweight primi-gravidas having body mass index (BMI) of < 18.5 kg/m$^2$.

The exclusion criteria included underweight primi-gravidas having any major illness such as gestational diabetes mellitus, pregnancy induced hypertension, thyroid diseases, liver diseases etc. or previously on any long-term medications and allergic to supplements. Also, those having any previous history of gastrointestinal anomalies, surgeries and any other eating disorders e.g. bulimia nervosa, anorexia nervosa and purging disorders were also excluded from the study.

**Sample size estimation:**

Sample size calculation was based on studies conducted by Fatima S. etal., on underweight females and Stratton RJ. etal., on healthy men receiving bolus tube feeding,[14,15] considering 85% power and CI of 95%, 24 participants were required to conduct this study. This sample size calculation was done using Open Epi® software.

**Participants' enrollment, intervention allocation & follow-up**

In our study, we screened 5210 women for eligibility as per study protocol (Figure 1). Out of these 3803 women were not meeting the criteria. Only 50 participants agreed to participate in the study and gave written informed consent. However, only forty participants were finally available to be randomized into intervention and placebo groups. Computer research randomizer (version 3.0) was used to randomly allocate the participants into LNS (intervention) group and placebo group.

Data was collected from 40 participants, 3 participants were lost during follow up visits due to different reasons and one sample was hemolysed. Data of 36 participants was finally analyzed.

**Data collection procedure**

A predesigned health questionnaire containing detail of medical history of pregnant woman was recorded from the participants. The socioeconomic data of each participant was also collected on a preformed sheet including information regarding their level of education, occupation and income etc.

Each participant of the study was asked to make a total of three visits at baseline, 16th week of gestation and post-natally for anthropometric, body composition measurements and 5 ml of fasting blood was taken at each time point and stored in EDTA tubes. The stored blood in the EDTA tube was used for hematological examination of hemoglobin, mean corpuscular volume (MCV) and hematocrit level. The hematological analysis was done using Sysmex XE-2100 hematology analyser (Sysmex Corporation, Shisumekkusu Kabushiki-gaisha, Japan). Height was measured by using a Portable stadiometer seca Leicester 214. The body weight and body composition was measured using Bioelectrical impedance scale (Beurer GmbH, Soflinger str.218 89077 Ulm, Germany Art._Nr.748.13, Type: Bf220).

**Treatment**

LNS group received 75 gms of high energy nutritional supplement, named "MAAMTA", made from peanut butter and contained 400 kcal/75gm of energy

**TABLE II: COMPARISON OF THE FETAL OUTCOMES OF THE PARTICIPANTS OF THE STUDY**

| Fetal outcome | LNS mean±SD | Placebo mean±SD | P-value |
|---|---|---|---|
| Weight (kg) | 2.84±.60 | 2.41±.61 | 0.042* |
| Crown heel length (cm) | 47.11±2.74 | 44.24±2.35 | 0.002** |
| Fronto-occipital circumference (cm) | 35.11±1.66 | 32.41±7.85 | 0.153 |
| Mid upper arm circumference (cm) | 11.89±1.15 | 11.18±1.28 | 0.086 |

Significant difference (*P<0.05, **P<0.01, ***P<0.001; LNS: Lipid bases nutritional supplement

while the placebo was made by taking 35 gms of wheat flakes plus 40 ml skimmed milk and 2 tablets of artificial sweetener (canderal) constituting 75 gm. It contained 137.8 kcal/75gm.

Allocation concealment was ensured by putting supplements in sequentially numbered, opaque containers. The participants were asked to consume one sachet of 75 gm LNS or placebo daily from their first visit after enrollment in the study till a week after delivery. Participants of both the groups were asked to consume the LNS/placebo in addition to their habitual diet and antenatal treatments throughout the pregnancy and one week after the delivery. The supplements were delivered by the main researcher on weekly basis. The participants were asked to keep with them the empty sachet of the LNS/placebo after utilization, which was collected by the prime researcher in the following week to measure the leftovers and determined the compliance of the participants. In addition to antenatal treatment and LNS/placebo the participants were provided with nutritional counseling. After 16th week of gestation and postnatal visit fasting blood was taken and tests were repeated, and the anthropometric measurement were also done. Moreover, incentives were given to the participants for their time and travelling expenses. All the measurements were obtained in a fasted state.

### Statistical Analysis

All data was collected and analyzed by using SPSS version 20. For comparison among the groups Student t-test was used. Chi-square test was used for comparing the obstetrical and demographic data of the groups.

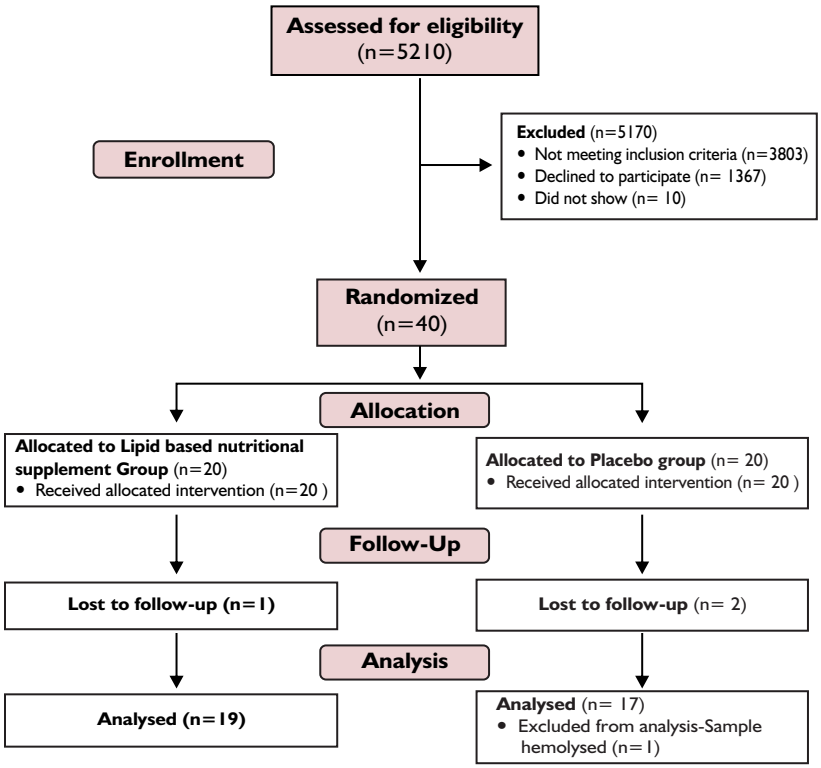


Figure 1: Flow chart showing enrolment of participants, intervention allocation, follow-up, and data analysis

## RESULTS

The age of the participants ranged from 15 to 25 years with mean of 18.85±2.49 years in the supplement group and 18.47±2.60 years in the control group and median 18 years indicating that 50% of the patients were from above 18 years of age group while a similar proportion was from below 18 years age group.

The BMI of the participants in the LNS group was 17.79±0.66 kg/m$^2$ and that of the placebo group was 17.44±1.05 kg/m$^2$ (p=0.634) on their first visit. Bio-electrical impedance scale was used to measure the body composition of the participants on each visit. The mean weight of the participants in the LNS group was 41.24±3.54 kg while it was 40.92±3.02 kg in the placebo group (P=0.774) while the rest of the parameters measured by the bioelectrical impedance scale were Hydration (LNS group; 51.6±5.84% and placebo group; 54.09±6.32%), Bone mass (LNS group; 32.9±5.18% and placebo group; 33.28±6.80%) and Mid upper arm circumference (MUAC) [LNS group; 21.29±1.41 cm and placebo group; 20.62±1.45 cm] as shown in Table I.

The morphological characteristics of the participants on second visit which was between weeks 12-20 are also shown in Table I. As compared to the findings of visit 1, there was significant increase in the weight, BMI, body fat & bone mass in the LNS group while almost no change in the hydration and MAUC measurement in this group. In the placebo group there was increase in the weight and BMI, almost no change in the MUAC while a decrease in the hydration and body fat was observed. As for the comparison amongst the groups, there was no significant difference among these parameters between the two study groups. At the postnatal visit made by the participants within a week of the delivery, the comparison of morphological features between the groups shows that there were significant changes between the groups as well as within the groups (Table I).

The effect of LNS on pregnancy outcomes showed majority (n=33/36; 91.7%) had normal vaginal deliveries (n=18/19 in LNS group and n=15/17 in

**TABLE III: COMPARISON OF THE HEMATOLOGICAL FINDINGS OF BOTH THE GROUPS ON THREE DIFFERENT VISITS**

| Visits | Lab. Parameters | LNS mean±SD | Placebo mean±SD | P-value |
|---|---|---|---|---|
| 1st: | Hemoglobin (g/dl) | 10.71±1.41 | 11.22±1.70 | 0.326 |
| | Mean corpuscular volume (fl) | 82.46±11.01 | 84.56±5.59 | 0.474 |
| | Hematocrit (%) | 34.84±3.52 | 32.63±6.34 | 0.197 |
| 2nd: | Hemoglobin (g/dl) | 10.76±1.45 | 11.16±1.31 | 0.395 |
| | Mean corpuscular volume (fl) | 82.78±11.52 | 83.54±4.94 | 0.803 |
| | Haematocrit (%) | 35.13±3.66 | 31.93±5.01 | 0.038 |
| 3rd: | Hemoglobin (g/dl) | 10.72±1.23 | 10.60±1.02 | 0.753 |
| | Mean corpuscular volume (fl) | 5.56±4.82 | 84.48±6.13 | 0.564 |
| | Hematocrit (%) | 33.66±5.84 | 33.44±4.57 | 0.905 |
| Neonatal Hematology | Hemoglobin (g/dl) | 10.74±1.19 | 10.55±1.07 | 0.623 |
| | Mean corpuscular volume (fl) | 85.85±4.85 | 84.77±6.02 | 0.555 |
| | Hematocrit (%) | 33.75±5.69 | 33.44±4.58 | 0.856 |

Significant difference (*P<0.05, **P<0.01, ***P<0.001), LNS (Lipid bases nutritional supplement)

placebo group). Frequency of Cesarean section was 1/19 (5.3%) in LNS group and 2/17 (11.8%) in placebo group. Abortion was not reported in any case.

The mean neonatal weight in the LNS group was 2.84±.60 kg as compared to the placebo group 2.41±.61 kg (p=0.042*). Mean crown heel length (CHL) was 47.11±2.747 cm and 44.24±2.359 cm in LNS and placebo groups respectively (p=0.002). There was no significant difference in both group with respect of mean fronto-occipital circumference and MUAC (Table II).

The hematological findings of the mothers at all the three visits showed no significant difference between the groups and within the groups at the visits in terms of mean concentration of hemoglobin, MCV and hematocrit level (Table III). The hematological analysis of cord blood drawn as a fetal index showed no significant difference between the two groups in hemoglobin, MCV and hematocrit concentrations.

## DISCUSSION

Body systems function properly if balanced amount of nutrients is taken.[16] The risk of hypertension, gestational anemia, miscarriages, pre-term delivery, fetal deaths and maternal mortality is increased with maternal malnutrition.[17] BMI before conceiving and pregnancy weight gain reflects maternal nutritional status both before and during pregnancy and are excellent fetal growth indicator.[18]

In terms of maternal outcomes, no significant effect of LNS supplementation on maternal weight gain or MUAC was observed during pregnancy. The effect of LNS on maternal weight gain was not as expected because the participants consumed only one sachet of 75 gms LNS per day containing about 400 kcal in contrast to the balanced protein-energy supplements that have shown a weight gain of up to 21 g/wk. in different trials conducted,[19] whereas we observed a difference of only 5 kg/visit. The reason was that the amount of energy provided by LNS as compared to protein energy supplements was very low. Although in a recent trial conducted in Tanzania on multivitamin intervention (without any macronutrients) have shown a promising effect of 15 g/wk. more in the supplement than the placebo group, this weight gain was also greater than our study's results.[20] Although the participants of both the groups continued to take their antenatal treatment including the supplements prescribed by the doctors in addition to LNS/placebo, their hematological results were not satisfactory. There may be several possible reasons for this low hemoglobin observed. First, may be the dose of iron that was used in our LNS supplements of 10 mg was too low for pregnant women in our population. A 60 mg/day of iron dose in the form of the iron plus folic acid supplement and 30 mg/day of iron in multiple micronutrient supplement were used in similar studies,[21,22] although studies conducted in Indonesia,[23] Nepal[24] and Tanzania[20] received iron doses of at least 50 mg/day. A study done on Australian women[25] suggested that for preventing Iron Deficiency Anemia (IDA) during pregnancy, 20 mg iron per day may be an ideal dose as compared with higher doses of iron. However, the women in our study are of lower socioeconomic background and joint family systems in which there are food insecurities.

In this study, the effect of LNS on birth outcomes as compared with the placebo group was not significant in contrast to the SUMMIT study done in Indonesia, in which women with poor nutritional status having anemia and low BMI were given multiple micronutrients and showed a good effect on birth outcomes.[26] It was also shown that the infants of women consuming Multiple Micro-Nutrients (MMN) supplements as compared to those of women who received iron-folic acid had an 18% reduction in early infant mortality. Similar results were shown in a study conducted in Bangladesh.[27] We also found that compared to placebo, LNS does not have any significant effect on reduction in the cesarean sections. These findings are consistent with the findings of another study also conducted in Bangladesh.[9]

In this study, a significant difference was observed on birth length of the neonates in the LNS group as compared to the placebo group, similar results were shown in a study by Mridah MK etal., in which the infants in the LNS group had a higher birth weight & length as compared to the iron-folic acid group.[28] In another randomized controlled trial by Huybert L etal, reported that the birth length [4.6 mm (95% CI: 1.8,7.3)] and placental weight [15.6 g (95% CI: 0.4, 30.7)] were significantly increased with LNS supplementation given on daily basis as compared to MMN supplements.[12] Although their study have shown increase in birth weight and head circumference as well, which was not observed in our study. However, similar effects of increase in birth length have

been shown with prenatal MMN supplementation[29] or balanced protein-energy supplementation.[30] They have also shown positive effect in contrast to our study on birth weight. The reason for this effect could be that the birth weight is influenced by maternal factors like height and parity. Other reasons could be the low maternal weight gain per visit in our study due to the nutrient deficient diet they consume and/or not absorbing sufficient calories due to morning sickness or lack of appetite due to progesterone.

Strengths of our study are low dropout rates, compliance of the participants maintaining high level of standardization and quality assurance during data collection because data was collected by the same investigator from all the participants. Limitations of our study are the small number of participants and short duration of the study as many studies have been continued till one year post-natally.

## CONCLUSION

The prenatal use of LNS increases the CHL of the neonates of underweight primi-gravidas and can be used as an intervention among underweight primigravida and pregnant women in non- emergency community setups as well as food insecure areas. However, no significant effect of LNS were observed on maternal gestational weight gain per visit, prevalence of maternal anemia, maternal mortality & neonatal birth weight in underweight primi-gravidas.

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## AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**KT:** Conception and study design, acquisition of data, drafting the manuscript, critical review, approval of the final version to be published

**SF:** Conception and study design, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

**RN & SHH & MS:** Analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

*Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

**CONFLICT OF INTEREST**

Authors declared no conflict of interest

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**DATA SHARING STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.