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SAFETY AND EFFECTIVENESS OF COMBINED CALCIUM, VITAMIN D3, AND B-VITAMIN SUPPLEMENTATION IN INDIAN PREGNANT WOMEN: RETROSPECTIVE REAL WORLD INDIAN STUDY

Medical Science

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ABSTRACT

Objective: Micronutrient deficiencies during pregnancy are associated with adverse maternal and fetal outcomes. This study evaluates the effectiveness and safety of combined supplementation with calcium carbonate, vitamin D3, methylcobalamin, L-methyl folate calcium, and pyridoxal-5-phosphate in pregnant women. **Methods:** A multicentric, retrospective, observational study was conducted across 273 healthcare facilities in India over an 18-month period (March 2023 to August 2024), enrolling pregnant females who received the combined supplementation. Demographic characteristics, medical history, supplementation regimen, pregnancy outcomes, and maternal and fetal health indicators were extracted from existing medical records. The statistical analyses were conducted employing SPSS software. **Results:** A total of 2,799 pregnant women with a mean maternal age of 28.8 years were included in the study. The majority of the females had full-term deliveries (89.92%). Preterm births occurred in 10.08% of pregnant women, while gestational hypertension, diabetes, and Intrauterine Growth Restriction (IUGR) were seen in 13.47%, 11.36%, and 9.75% of cases, respectively. Mean maternal blood pressure was 123.7 ±10.6 / 85.7 ±16.1 mmHg. Hemoglobin levels averaged 10.0 g/dL ±4.0, and 79.35% of participants had negative urinary protein tests. Neonatal mean birth weight and average age at gestation were 2425.6 g ±567.4 and 32.2 ±11.1weeks, respectively. The mean APGAR scores at one and five minutes averaged 7.2 ±1.7. No adverse events were reported. **Conclusion:** The combined supplementation was found to be effective and well-tolerated, supporting favorable maternal and fetal outcomes during pregnancy.

KEYWORDS

Pregnancy Outcomes, Newborn Outcomes, APGAR score

INTRODUCTION

Pregnancy is an important period during which maternal nutritional status had profound impacts on both, maternal and fetal health. In the course of pregnancy, females are predisposed to developing nutritional deficiencies. Adequate micronutrient intake during the periconceptional period and throughout gestation is important for regulating maternal health and supporting fetal organ development.[1] Fetal health is determined by the status of maternal health, as the fetus relies entirely on maternal nutrition for its growth and development.[2,3]

Among the essential nutrients crucial for supporting maternal wellbeing and fetal development, are calcium, vitamin D3, methylcobalamin, L-methyl folate calcium, and pyridoxal-5-phosphate. Each nutrient has a unique role in maternal and fetal health. The WHO (World Health Organization) and India's Maternal Health Division recommend calcium supplementation during pregnancy, especially for low-calcium diets, to reduce the risk of maternal hypertension, complications, and mortality.[4,5]

Vitamin D aids in the absorption and utilization of calcium, ensuring optimal bone mineralization and supporting immune function.[6] Vitamin D deficiency impairs maternal and fetal calcium metabolism, resulting in neonatal hypocalcemia and tetany, maternal osteomalacia, and tooth enamel hypoplasia in infants.[1] Methylcobalamin, the active form of vitamin B12, has significant importance in optimal activity of various physiological functions, including DNA synthesis, neurological function, and red blood cell production. Deficiency in vitamin B12 during pregnancy may result in maternal anemia and neural tube defects in the child at birth.[7]

Folic acid supplementation during pregnancy is crucial to help prevent neural tube defects in the developing baby.[8] Lastly, pyridoxal-5-phosphate, the active form of vitamin B6, contributes to amino acid metabolism, neurotransmitter synthesis, and immune function, thereby supporting maternal health and fetal development.[9]

Pregnancy-related nutritional challenges may be managed with combined supplementation of calcium, vitamin D3, methylcobalamin, L-methyl folate calcium, and pyridoxal-5-phosphate. However, limited data exist on its safety and efficacy. This retrospective study evaluates its impact on pregnancy outcomes, maternal health, and adverse events to support evidence-based clinical practice and optimize maternal-fetal health.

METHODS

Study Design

The present multicentric retrospective observational study aimed to evaluate the effectiveness and safety of combined supplementation during pregnancy. Data was collected over an 18-month period (March 2023 to August 2024) from 273 healthcare facilities across India, including hospitals, obstetric clinics, and prenatal care centers. Ethical approval was obtained from the life Point Research Ethics Committee, Pune. Informed consent from patients was waived, as the study involved anonymized retrospective data.

Study Population

Maternal health records were screened to include pregnant women who received combined micronutrient supplementation and had complete health data. Exclusion criteria included incomplete records, pre-existing hypercalcemia, conditions affecting calcium/vitamin D metabolism, and CKD stage 4 or higher.

Outcome Measures

Anonymized patient data on demographics, medical history, supplementation, and health outcomes were extracted from existing records. The study focused on pregnancy-related adverse events, neonatal outcomes (birth weight, gestational age, Apgar scores), maternal indicators (BP, hemoglobin, urinary protein, delivery mode), and adherence tracked via refill records and self-reports.

Data Analysis

Statistical analysis was performed using SPSS at a 95% confidence interval. Descriptive statistics summarized demographics, outcomes, and adverse events, with categorical variables presented as frequencies and percentages, and continuous variables as mean ± SD; $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Clinical characteristics at baseline and demographic data are outlined in Table 1. A total of 2,799 pregnant women with a mean maternal age of 28.8 ± 5.2 years were included in the study. The mean weight and height of the total study population was 45 ± 6.1 kg and 152.3 ±9.6 cm, respectively.

The majority of participants (68.88%) were asymptomatic at presentation, while a small proportion reported back pain (9.25%),

weakness (6.5%), and backache (5.14%). Participants had a mean parity of 1.0 ±0.7 , with supplementation initiated at an average gestational age of 16.2 ±11.5 wks.

Table 1: Patient Demographic And Characteristic Data

Demographic	**Mean**	**SD**
Baseline Maternal Age	28.8	5.2
Weight	45.2	6.1
Height	152.3	9.6
Presenting Complaints	**n**	**%**
None	1938	68.88%
Back Pain	259	9.25%
Weakness	182	6.50%
Backache	144	5.14%
Vomiting	114	4.07%
Fever	4	0.14%
Pregnancy-Related Indicators	**Mean**	**SD**
Parity (Number of previous pregnancies)	1	0.7
Gestational Age at Initiation of Supplementation (Weeks)	16.2	11.5

Supplementation Regimen Compliance

Compliance with supplementation was reported as 63.59% through prescription refill records and 36.41% via self-reported adherence.

Pregnancy Outcomes

Most females (89.92%) had full-term deliveries, while 10.08% experienced preterm births. Gestational hypertension, gestational diabetes, and intrauterine growth restriction were noted in 13.47%, 11.36%, and 9.75% of the participants, respectively (Table 2).

Newborn Outcomes

Newborns had a mean birth weight of 2425.6 ± 567.4 g, which falls within the normal range.. Apgar scores at one and five minutes averaged 7.2 ±1.7, reflecting adequate neonatal health (Table 2).

Maternal Health Indicators

The mean weight gain during pregnancy was 7.8 ± 4.3 kg. The average gestational age at the time of delivery was 36.74 ± 5.36 wks. Mean maternal blood pressure was 123.7 ±10.6) / 85.7 ±16.1) mmHg. Hemoglobin levels averaged 10.0 g/dL ±4.0 , and 95.5 % of participants had negative urinary protein tests, indicating good overall maternal health during pregnancy (Table 2).

Table 2: Fetal And Maternal Outcomes Following Combined Supplementation Intake

Adverse Pregnancy Outcomes	**n**	**%**
Preterm Birth	282	10.08
Gestational Hypertension	377	13.47
Gestational Diabetes	318	11.36
Intrauterine Growth Restriction	273	9.75
Maternal Health Indicators	**Mean**	**SD**
Maternal Weight Gain During Pregnancy (kg)	7.8	4.3
Gestational Age at Delivery (weeks)	36.74	5.36
Blood Pressure - Systolic (mmHg)	123.7	10.6
Blood Pressure - Diastolic (mmHg)	85.7	16.1
Hemoglobin Levels	10.0	4.0
Urinary Protein (Positive)	294	10.50
Mode of Delivery	**n**	**%**
Cesarean section	1260	45.02
Vaginal	1539	54.98
Newborn Characteristics	**Mean**	**SD**
Birth Weight (grams)	2425.6	567.4
Apgar Scores (1 and 5-minute scores)	7.2	1.7

Adverse Effects

Most of the patients did not report any adverse effects (93.5%). Only 6.5% of patients reported minor adverse events, with gastrointestinal symptoms (Nausea, vomiting, constipation, Gastric irritation) being the most common (4.7%).

DISCUSSION

Our study found that combined supplementation of calcium, vitamin D3, methylcobalamin, L-methyl folate calcium, and pyridoxal-5-phosphate was linked to a reduction in adverse pregnancy outcomes and improved maternal and neonatal health indicators.

Present study found a pre-term birth rate of approximately 10%, significantly lower than the 18% prevalence reported by the National Family Health Survey (NFHS-5) 2019–21 in India.[10] A meta-analysis showed that high serum folate levels in pregnant females reduce preterm birth risk by 28%, and adequate folic acid supplementation resulted in a 10% lower risk of preterm birth.[11] A large-scale retrospective analysis of pregnant women demonstrated that daily 500 mg calcium supplementation for over six months significantly lowers the risk of presenting with hypertension.[12] Vitamin D supplementation can help in preventing pre-eclampsia, with higher doses providing greater benefits.[13]

Gestational diabetes is a common condition during pregnancy that may be effectively prevented through combined micronutrient supplementation, as observed in the present study. Several meta-analyses support the role of vitamin D supplements for reducing blood glucose and improving lipid profiles, and inflammatory markers.[14,15] Given the impact of vitamin D on gestational diabetes, vitamin D supplementation could serve as a preventive strategy in pregnant women.

Intrauterine growth restriction was reported in 9.75% of the pregnant women in the present study. This rate is lower than the global prevalence of 10–15%.[16] Inadequate levels of Vitamin D are a significant risk factor for intrauterine growth restriction.[17] Vitamin D promotes healthy placental development and function. Therefore, inadequate vitamin D intake increases the risk of placental inflammation, which can impair placental function and contribute to adverse pregnancy outcomes.[1,2]

The study found an average birth weight of 2450 g, above the threshold of low birth weight provided by the WHO (<2500 g), indicating positive fetal outcomes.[18] A small percentage of participants showed proteinuria, a marker of preeclampsia detected during antenatal screening. While not directly studied, the combined micronutrient supplementation may help reduce proteinuria risk by improving blood pressure and managing hypertension.[1]

Overall, the study highlights the positive impact of combined supplementation on maternal and neonatal health, aligning with WHO recommendations for calcium, vitamin D, and folic acid intake during pregnancy.[1-3]This combined formulation may enhance compliance and therapeutic outcomes, offering a practical approach to improving pregnancy care.

This multicentric study involved a large number of participants across various regions in India, enhancing the generalizability of its findings to the broader Indian population. It provides valuable insights into the safety and efficacy of combined supplementation with calcium, vitamin D3, methylcobalamin, L-methyl folate calcium, and pyridoxal-5-phosphate—an area not well studied in Indian clinical settings.

However, the study has certain limitations. The absence of a comparator arm restricts the evaluation of relative efficacy, and low adherence may have led to an underestimation of the supplementation's benefits. Additionally, unmeasured confounding factors such as diet, lifestyle habits, and comorbidities may have influenced the outcomes. Future RCTs are required to confirm these findings by comparing the combined supplementation regimen with either placebo or other standard practices.

CONCLUSION

The combined supplementation demonstrated good effectiveness and safety, with favorable maternal and fetal outcomes observed. Additionally, no adverse events related to the combined supplements were observed.

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