A Comparative Study to Evaluate the Impact of Vitamin D Supplementation on the Outcome of Pregnancies with Intrauterine Growth Retardation

Suhagini Murmu[1], Anit Jaiswal[2], Chandrajyoti[3], Naaz Ahmed[4]

ABSTRACT

Introduction: Maternal vitamin D deficiency is a major public health problem. Poor vitamin D status during pregnancy is associated with poor outcomes and increased morbidity. The present study was conducted to find any association between maternal vitamin D3 deficiency and IUGR and impact of Vitamin D3 supplementation on the outcome.
Material and Methods: This prospective, randomised, double blind, interventional study was conducted on 172 pregnant women diagnosed of Type II/Type III IUGR and confirmed by ultrasound. They were randomly divided into two Groups: Group A (supplemented with Vitamin D 2000 IU/day) and Group B (no supplementation). All the cases were followed up till delivery and any significant events were recorded.
Results: Statistically significant differences were found in the caesarean section rates and birth weights of the neonate in both the Groups. There was no significant impact on duration of gestation. Moderately positive correlation was found between the duration of supplementation and increase in birth weight.
Conclusion: Maternal Vitamin D3 deficiency is associated with increased risk of operative delivery and low birth weight, both of which can be improved by Vitamin D supplementation. The increase in birth weight correlates with the duration of supplementation.

Keywords: Birth Weight, Caesarean Section, Calcium, Gestational Age, Intrauterine Growth Retardation, Vitamin D.

INTRODUCTION

Maternal vitamin D deficiency is a major public health problem.[1] Globally, nearly 80% to 90% population are vitamin D deficient. Vitamin D deficiency is prevalent even in settings of widespread prenatal vitamin use[2], because prenatal vitamins contain doses of vitamin D that are too low to meaningfully raise serum 25-hydroxyvitamin D[3].
Poor vitamin D status during pregnancy has been associated with preeclampsia, gestational diabetes, and bacterial vaginosis, preterm labour and IUGR as well as offspring rickets reduced bone density, asthma and schizophrenia. The inconsistency of past findings may be related to the study of continuous birth size rather than a pathologic condition such as growth restriction, or the varied populations studied and methods used. Furthermore, the majority of studies conducted in past examined the effect of vitamin D in the 3rd trimester of pregnancy, when fetal growth velocity is greatest[4]. Yet, evidence indicates that fatal growth trajectory in late gestation is determined much earlier, most likely in early pregnancy.[5]

Pregnant women in India have been shown to have up to 84% prevalence of Vitamin D Deficiency which correlated significantly with serum Vitamin D3 status of their new born. Mothers with suboptimal vitamin D3 status have off springs with reduced intrauterine and postnatal skeletal development.[6]
Various studies conducted to correlate the vitamin D deficiency with Intrauterine Growth Retardation (IUGR) have shown varying results as many studies directly correlated fetal growth with vitamin D supplementation in vitamin D deficient groups others could not found any correlation.
The present study was conducted with the aim to find any association of vitamin D3 deficiency with IUGR and whether supplementation of vitamin D3 in the deficient group has any impact on the outcome of the pregnancy.

MATERIAL AND METHODS

This prospective, randomised, double blind, interventional study was conducted in the Department of Obstetrics and Gynecology, Pt. J. N. M. Medical College and associated Dr. B.R.A.M. Hospital Raipur among the pregnant women (gestation age more than 24 weeks), diagnosed as IUGR who attended or were admitted in the department of Obstetric and Gynecology. Sonographic confirmation of IUGR was the inclusion criteria. The exclusion criteria included: Anemia, APH, Placenta previa, Pre-eclampsia, Hepatic or renal failure, Diabetes mellitus, Multiple gestations, Parathyroid and adrenal diseases, Rheumatoid disorder, Mal-absorption, Bone disorder and any drugs affecting absorption of vitamin D3 and calcium. A written informed consent was obtained

[1]Senior Resident, Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Patna, Bihar, [2]Consultant (Obstetrics and Gynecology), Jaiswal Maternity Home, Pathalgaon, Chhattisgarh, [3]Senior Resident, Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Patna, Bihar, [4]Senior Resident, Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Patna, Bihar, India

Corresponding author: Dr. Anit Jaiswal, 4/133, Agrasen Bhavan Marg, Ambikapur Road, Pathalgaon, Jashpur (Chhattisgarh) - 496118, India

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from all the patients. A total of 172 women were included in the study which were randomly divided into two Groups:
Group A: Supplemented with Vitamin D (2000 IU/day) till the time of delivery
Group B: No supplementation given
Detailed history (including menstrual and obstetric) was taken. Examination was done as per protocol. Routine investigations were done. In addition, serum vitamin D3 level (ELISA) and serum calcium levels were monitored.
Deficiency levels were considered as: Serum Vitamin D less than 50 nmol/L or Serum calcium less than 8 mg/dL.
All the cases were regularly followed up throughout their rest of pregnancy. At the time of delivery blood samples were taken to assess vitamin D3 level, calcium level and alkaline phosphatase level. Mode of delivery, feto-maternal outcome, and any significant intranatal or postnatal events were recorded.

STATISTICAL ANALYSIS

The data was analysed by SPSS: Student t-test for quantitative data and Chi square test (Fisher's exact test when any cell value was less than 5) for qualitative data. Correlation was determined by the Pearson correlation test and the strength was interpreted as:

- Less than 0.3: None or Very Weak
- 0.3 to 0.5: Weak
- 0.5 to 0.7: Moderate
- More than 0.7: Strong

P value of less than 0.05 was considered to be statistically significant.

RESULTS

Both the Groups were comparable in terms of demographic variables. The overall incidence of IUGR was 8% (586 out of total 6789 deliveries). The difference in the distribution of Type II and Type III IUGR between the two Groups was not statistically significant (*P value: 0.26*) (Table 1).
The maternal serum Vitamin D and Calcium levels were almost similar in the two Groups (*P values of 0.45 and 0.73*). However, after supplementation, both, serum Vitamin D and

Parameter	Group A	Group B	P value	Statistical Significance
Type II IUGR	77	72	0.26	Not Significant
Type III IUGR	9	14		

Table-1: Distribution of Type II and Type III IUGR in the two Groups

Parameter		Group A (Mean ± SD)	Group B (Mean ± SD)	P value	Statistical Significance
Before Supplementation	Vitamin D (in nmol/L)	25.87 ± 11.36	27.10 ± 10.12	0.45	Not significant
	Serum Calcium (in mg/dL)	8.64 ± 1.20	8.58 ± 1.01	0.73	Not significant
After Supplementation	Vitamin D (in nmol/L)	62.92 ± 12.16	27.10 ± 10.12	<<0.0001	Significant
	Serum Calcium (in mg/dL)	10.07 ± 0.85	8.58 ± 1.01	<<0.0001	Significant

Table-2: Comparison of Serum Vitamin D and Calcium levels in the two Groups.

Parameter	Group A	Group B	P value	Statistical Significance
Operative delivery (LSCS)	37	52	0.022	Significant
Spontaneous/induced	49	34		

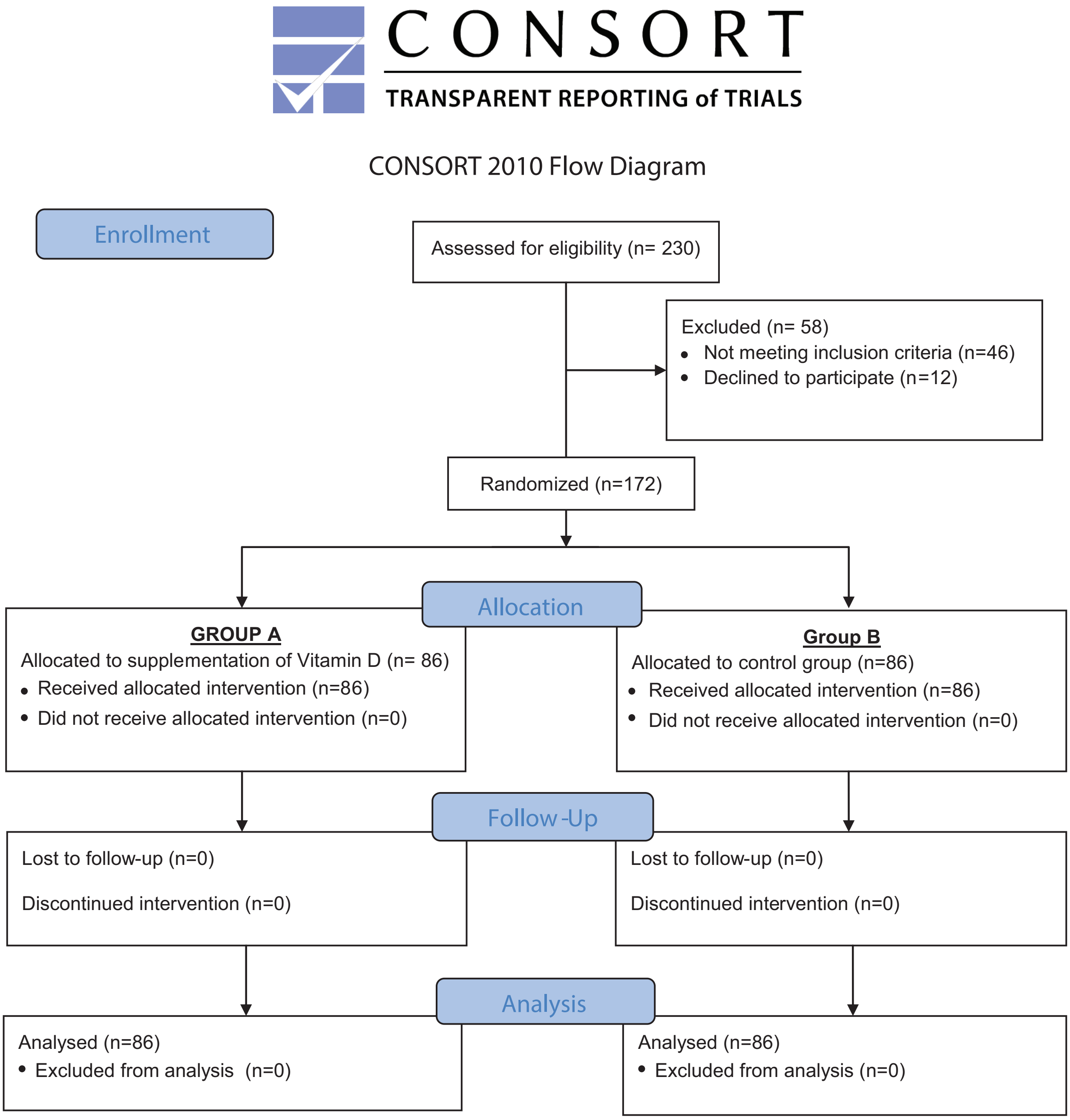
Table-3: Comparison of requirement of operative delivery (LSCS) in the two Groups (after supplementation in Group A)

Parameter	Group A (Mean ± SD)	Group B (Mean ± SD)	P value	Statistical Significance
Time of delivery (in weeks)	38.71 ± 1.59	38.37 ± 1.74	0.186	Not Significant
Birth weight (in kgs)	2.65 ± 0.41	2.27 ± 0.43	<<0.0001	Significant

Table-4: Comparison of time of delivery and birth weight in the two Groups (after supplementation in Group A)

Parameter 1	Parameter 2	Pearson coefficient	Interpretation	P value	Statistical Significance
Birth weight at the time of diagnosis	Percentage increase in birth weight	-0.74	Moderately strong negative correlation	<<0.0001	Significant
Duration of supplementation	Percentage increase in birth weight	0.67	Moderately strong positive correlation	<<0.0001	Significant

Table-5: Correlation of the various parameters in the two Groups



Calcium levels were more in the Group A as compared to the Group B and this difference was statistically significant (Table 2).

The average duration of supplementation of Vitamin D in the Study Group was 6.43 ± 3.22 weeks. The requirement of operative delivery by caesarean section (LSCS) in the Group A was significantly less after supplementation as compared to the Group B (Table 3).

The mean time of delivery in both the Groups was around 38 weeks, with no statistically significant difference (Table 4).

The mean birth weight was significantly more in the Group A than in the Group B. (Table 4). The average increase in birth weight (as determined by ultrasound at the time of diagnosis to the actual birth weight of the neonate) was 115% ± 101%. Moderately strong negative correlation (correlation coefficient = -0.74) was found between the estimated birth weight determined by ultrasound at the time of diagnosis and the percentage increase in birth weight after Vitamin D supplementation, indicating that the lesser the birth weight more was the percentage increase after supplementation. This correlation was statistically significant (*P value <0.0001*).

Moderately strong positive correlation (correlation coefficient = 0.67) was also found between the duration of Vitamin D supplementation and the percentage increase in birth weight after supplementation, indicating that the more the duration of supplementation, more was the percentage increase after supplementation. This correlation was statistically significant (*P value <<0.0001*).

DISCUSSION

IUGR is defined as a fetus born with birth weight less than the 10^{th} percentile of birth weight for gender specific growth reference curve. Over all incidence of IUGR is 2-10% in general population in most of the developing countries.[7] In

India the incidence of IUGR is 2-8% among all pregnant women.[8]

The IUGR can be classified in 3 groups-

1. Type I IUGR (Symmetrical IUGR)
2. Type II IUGR(Asymmetrical IUGR)
3. Type III IUGR (Type I + Type II).

While Type I IUGR is mostly caused due to an early insult to the multiplication of the fetal cells, indicating the involvement of intrinsic pathological processes, Type II and Type III IUGR are caused by extrinsic factors like most of micronutrient deficiency. Thus, in the latter Types growth retardation develops after 2nd trimester.[9] Therefore, in this study only the Type II and Type III IUGR cases were included to evaluate the effect of Vitamin D supplementation.

Maternal Vitamin D and calcium levels: 84%-90% 0f Indian pregnant women are suffering from hypo-vitaminosis.[6] In present study 95.9% women were deficient of vitamin D3 as their level of vitamin D3 at the time of diagnosis of IUGR was below less than 50 nmol/L. Only 3.4% women found vitamin D insufficient whose vitamin D3 level was between 50-75 nmol/L.

The maternal serum Vitamin D and Calcium levels were significantly higher in the supplemented Group. This was comparable to the systematic review by Pérez-López et al[10], which involved 13 RCTs involving supplementation of Vitamin D alongwith other micronutrients. They also found higher circulating levels of Vitamin D at term. This was also similar to the study by Hollis et al[11] and Hossain et al[12].

Time of delivery: No significant differences were found in the time of delivery after Vitamin D supplementation. This was comparable to the study by Hossain et al[12].

However, most of the births were at term in both the Groups. De Regil et al[13] found that Vitamin D supplementation significantly reduces the preterm birth (3 trials involving 477 patients).

Incidence of operative delivery: There was a significantly decreased requirement of operative delivery (LSCS) after Vitamin D supplementation. This was comparable to the study by Merewood et al[14], who found the risk of requirement of caesarean section to be almost 4 times in the Vitamin D deficient women than the non-deficient ones. They speculated that the serum calcium levels play an important role in the early initiation of labor. And since Vitamin D is responsible for the maintenance of serum calcium levels, therefore, very low levels of Vitamin D (less than 37 nmol/L) may delay the onset of labor.

This was in contrast to the systematic review by Pérez-López et al[10], who found that Vitamin D supplementation does not affect the requirement of caesarean section. Similar was the conclusion by De Regil et al[13].

Birth weight: There was a significant increase in the birth weight of the babies after Vitamin D supplementation to the mothers. This was comparable to the observation in the systematic review by De Regil et al[13], it was found that Vitamin D supplementation reduces the incidence of low birth weight babies (less than 2500 grams). Similar was the conclusion of the systematic review by Pérez-López et al[10] and Maugeri et al[15]. The latter hypothesized that this might be due to the fact that sufficient levels of vitamin D are required to maintain adequate levels of calcium and phosphate. This, in turn, enables the critical processes of bone mineralization and development during fetal life. Also, the active form of Vitamin D may regulate the genes responsible for the proper implantation of the placenta.

Limitations: As the study was limited to the indoor admissions of the pregnant women with IUGR, therefore, the results may not be generalised.

CONCLUSION

The maternal serum levels of Calcium maybe normal despite low Vitamin D due to the complex interplay of various factors. Maternal deficiency of Vitamin D is significantly associated with increased risk of operative delivery and the increased incidence of low birth weight, which can be improved by Vitamin D supplementation. The increase in birth weight correlates directly with the duration of supplementation and has a negative correlation with the baseline estimated birth weight.

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