The Egyptian Journal of Hospital Medicine (October 2023) Vol. 93, Page 6996-7001

Maternal Vitamin D deficiency and Intra Uterine Growth Retardation

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ABSTRACT

Background: Numerous epidemiological research point to a connection between fetal intrauterine growth restriction (IUGR) and vitamin D deficiency (VDD). **Objective:** The point of the present examination is to research the vitamin D status and find if there is a relationship between maternal vitamin D insufficiency and intra uterine growth restriction (IUGR). **Subjects and Methods:** From February to August 2019, our case-control study was carried out in the Maternity Hospital of Ain Shams University, it included 80 pregnant ladies (40 of them with IUGR and the other 40 with normal fetal growth). Included pregnant ladies were sampled for vitamin D level. Vitamin D test: By using the DRG® 25-OH D (complete) ELISA (EIA-5396), all samples were examined.

Results: Our investigation indicated significant connection between maternal vitamin D status and IUGR. Results here uncovered that maternal hypovitaminosis D is related with IUGR. **Conclusion:** Maternal vitamin D level ought to be estimated during pregnancy. Pregnant ladies ought to be urged to get normal sources of vitamin D, for example, satisfactory sun presentation, eating nourishment wealthy in vitamin D. Royal college of obstetricians and gynaecologists (RCOG) proposals with respect to vitamin D supplementation ought to be satisfied.

Keywords: Vitamin D deficiency; Intra Uterine Growth Retardation.

INTRODUCTION

Fetal growth restriction (FGR) is a typical and complex clinical issue, which is associated with significant risk of perinatal poor outcome. Notwithstanding irresistible causes and inherent contortions, FGR has been recognized as a significant supporter of perinatal mortality [(1)].

Up to 10% of pregnancies may be affected by intrauterine growth restriction, which is frequently referred to as small for gestational age (SGA), intrauterine development confinement (IUGR) or fetal development limitation (FGR) in a conflicting and befuddling way. Generally, an expected fetal weight (EFW) or abdominal circumference (AC), which is also referred to as stomach perimeter underneath the tenth centile, raises worries over problematic intrauterine development. Anyway, the qualification among typical and pathologic development frequently can't dependably be made at this subjective cut-off. Also, around 70% of embryos beneath the tenth centile will have a typical perinatal result [(2)]. The danger of bad outcome is corresponding to the level of development limitation with those underneath the third centile as well as abnormal umbilical course Doppler estimations at most serious danger of horribleness or mortality [(3)].

What's more, investigation of fetal development directions has been distinguished as a significant factor in the separation between physiological SGA and neurotic IUGR [(3)]. Vitamin D, a secosteroid hormone known for its old style, works in calcium take-up and bone digestion, is currently all around perceived for its non-traditional activities, including balance of inborn resistant reaction and guideline of cell multiplication [(4)].

Vitamin D lack is basic in pregnant ladies and is progressively perceived as a worldwide general medical issue. Expanding proof exhibits that vitamin D inadequacy during pregnancy is connected with gestational diabetes mellitus, pre-eclampsia, and bacterial vaginosis [(5)].

An efficient survey of writing featured the impact of vitamin D on birth weight. Vitamin D has a key job in fetal development by its association with parathyroid hormone and calcium homeostasis [(6)]. High commonness of vitamin D lack (around a billion) has been seen among individuals everywhere throughout the world [(7)].

The point of the present examination is to research the vitamin D status and find if there is a relationship between maternal vitamin D insufficiency and intra uterine growth restriction (IUGR).

SUBJECTS AND METHODS

At the Maternity Hospital of Ain Shams University, this case control study was carried out between February 2019 till August 2019, it included 80 pregnant ladies who were divided into 2 groups (group A which included 40 cases with IUGR and group B which included 40 pregnant women with normal fetal growth), they were recruited for from those women attending outpatient clinic of ASUMH after fulfilling inclusion criteria. The study comprised women aged from 20 to 35 years, with singleton pregnancy and gestational age between 28 – 34 weeks. Pregnant ladies with the following criteria were excluded from the study: drug misuse (cocaine), chronic kidney illness, hepatic disappointment, multiple pregnancy, congenital fetal malformation, antiphospholipid disorder, systemic lupus

Received: 15/03/2023
Accepted: 14/05/2023

erythematosus (SLE), thrombophilia, preeclampsia or eclampsia, diabetes mellitus.

Sampling:

Test size was determined utilizing STAT program, setting type-1 mistake (α) at 0.05 and force (1-β) at 0.8. Result from past investigation[8] demonstrated that in LBW moms mean vitamin D was 25.05 ± 20.16 ng/ml, while in ordinary gathering moms it was 38.13± 18.5 ng/ml. Estimation dependent on these qualities delivered a negligible example size 80 cases (40 cases for every gathering) subsequent to taking in thought 10% drop out rate. We obtained an informed consent from each woman participating in our study then history was taken, which comprised personal, obstetric, medical, and surgical histories as well as the past menstrual cycle. Examination: General examination included blood pressure, heart rate and temperature. Bilateral lower limb examination was performed. Abdominal examination included inspecting fundal levels and any previous scar, palpation of fundal level to detect gestational age using ulnar border of left hand, fundal grip to detect presentation using palm of both hands, umbilical grip to detect position using both hands placing on both sides of uterus at level of umbilicus, pelvic grip to confirm position, and auscultation of fetal heart sound. U/S was used for confirmation of gestational age, presentation, and viability.

Assessment of gestational age was calculated by knowing LMP or first trimesteric ultrasound.

Group A, where there was intrauterine growth restriction, which was analyzed by fundal level less than period amenorrhea and fetal abdominal circumference evaluated fetal growth underneath tenth centile as confirmed by sequential U/S done 3 weeks apart.

Serial ultrasound biometric measures were done, both as individual measures, as proportions, consolidated (as EFW) beneath tenth centile. Utilization of tenth centile was wise to sensitivities and specificities than other generally utilized centiles. Group B in which there was typical fetal weight, which was analyzed by fundal level equal to period of amenorrhea. Normal sequential ultrasound biometry was done.

Vitamin D test: By using the DRG® 25-OH D (complete) ELISA (EIA-5396), (Biocheck company, South San Francisco, California, USA) all samples were examined.

Intended Use: The DRG 25-OH D (complete) ELISA, a compound immunoassay, was utilized for estimation of absolute 25-OH D (Vitamin D2 D3) in serum.

Specimen assortment planning:

5 ml of blood were drawn through venipuncture into test tubes to collect the serum, which was centrifuged at room temperature without the use of an anticoagulant and allowed to thicken. We didn't access before complete thickening. Blood samples at that point were moved to be solidified at -20°C with reference of deficiency as >10 ng/ml, inadequacy as10-30 ng/ml, and ideal level as 30-100 ng/ml).

Ethical and legal aspect: **Detailed informed written consent was given to participants including their rights, nature, objectives, benefits and hazards of the study in a form understandable for her in Arabic language containing all locally required data and specifications. The original form was signed by personally dated signature, then retained by the investigator. If any woman was unable to read, oral presentation and explanation of the written consent in the presence of impartial witness was available. Alternatively, the participant could use the thumbprint or a mark in presence of witness who would also sign and personally date it. Nothing done till a valid consent was obtained.**

All reports, evaluation forms didn't contain any personal data to ensure their confidentiality. Only patient number and initials were recorded, and if the name of patient was appearing in any document, its privacy was kept by the investigator who had the personal identification list.

The protocol and any corresponding element according to the local regulations was approved before the beginning of the study by the Obstetrics and Gynaecology Department Council, Medical Faculty, Ain Shams University. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

Statistical analysis: Data were loaded into the computer using the IBM SPSS software programme, version 20.0, for the statistical analysis of the data. Number and percentage were used to describe qualitative data. The Chi-square test was used to compare differences in categorical variables between several groups. Mean and standard deviation were used to explain quantitative data for regularly distributed data, and median, minimum, and maximum were used to communicate data with an aberrant distribution. For normally distributed data, the independent t-test was used to compare two independent populations, and the F-test (ANOVA) was used to analyse more than two populations. Results of significance tests are expressed as two-tailed probability. At the 5% level, significance of the results was determined. At p 0.05, correlation was deemed significant.

RESULTS

- **Descriptive data:** The following tables and figures display data of the 80 pregnant women who participated in the study:
- **Clinical data:** Table 1 shows that P2 was the most common among the studied ladies.

Table (1): Age, gestational age, and parity among the 80 pregnant women

Variables		Frequency (%)
Age (years)		26.5 ± 4.53*
Gestational age (weeks)		30.78 ± 2*
Parity	P1	24 (30%)
	P2	31 (38.7%)
	P3	11 (13.8%)
	P4	2 (2.5%)
	P5	1 (1.3%)
	PG	11 (13.8%)

* Mean ± SD, PG: primi gravida.

Laboratory data:

Table (2): Laboratory data among the studied 80 pregnant women

Variables		Mean ± Standard deviation or Frequency (%)
Vitamin D level (ng/ml)		24.6 ± 15
Vitamin D categories	Deficiency	24 (30%)
	Insufficiency	23 (28.7%)
	Sufficiency	33 (41.2%)

Table 2 shows that only 41.2% of the studied women had sufficient D.

Comparative studies:

Clinical data:

Comparison of the two groups found no statistically significant differences in age, gestational age and parity ($p > 0.05$).

Table (3): Comparison of the clinical data of the two studied groups

Variable		IUGR group (40)	Normal group (40)	Mann-Whitney's U test
		Median (IQR)	Median (IQR)	P value
Age (years)		25 (21 – 28.5)	28 (24 – 30.5)	= 0.057
Gestational age (weeks)		30.5 (29 – 32.5)	30.5 (29 – 32)	= 0.751
Variable		**IUGR group (40)**	**Normal group (40)**	**Chi square test**
				P value
Parity	P1	12 (30%)	12 (30%)	= 0.5211
	P2	14 (35%)	17 (42.5%)	
	P3	6 (15%)	5 (12.5%)	
	P4	0 (0%)	2 (5%)	
	P5	1 (2.5%)	0 (0%)	
	PG	7 (17.5%)	4 (10%)	

IQR: inter-quartile range.

Laboratory data: A comparison between the two groups showed a significant statistical difference between the IUGR group and the normal group in terms of the D level. There was also a highly significant rise in the category of vitamin D deficiency in the IUGR group as compared to the normal group (Table 4 and Figures 1).

Table (4): Comparison of laboratory data between the two groups

Variable		IUGR group (40)	Normal group (40)	Mann-Whitney's U test
		Median (IQR)	Median (IQR)	P value
Vitamin D level (ng/ml)		13.8 (7.3 – 26)	36.5 (18.1 – 41)	= 0.00012**
Variable		**IUGR group (40)**	**Normal group (40)**	**Chi square test**
				P value
Vitamin D categories	Deficiency	19 (47.5%)	5 (12.5%)	= 0.0002**
	Insufficiency	13 (32.5%)	10 (25%)	
	Sufficiency	8 (20%)	25 (62.5%)	

**: Highly significant

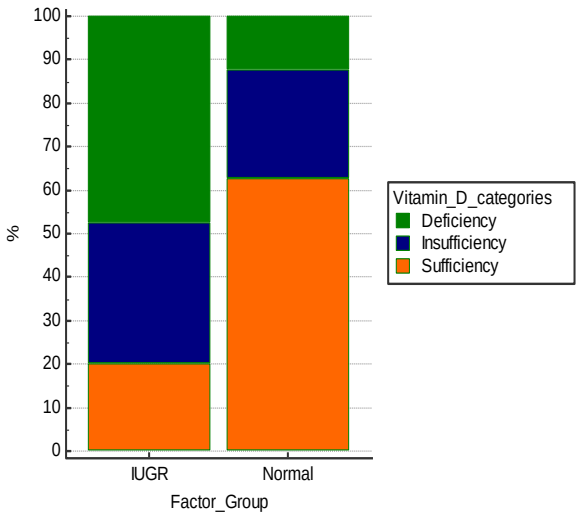

Figure (1): Comparison between 2 groups as regards vitamin D categories

Correlation studies:

The relative independent predictors (basic clinical factors, IUGR) of vitamin D outcomes were correlated using multiple logistic regression analysis and Spearman's correlation coefficient, where appropriate

No clinical condition had a significant link with vitamin D level according to Spearman's correlation analysis (Table 5).

Table (5): Spearman's correlation analysis of factors associated with vitamin D level

Associated Factor	Vitamin D level	
	Rho	P
Age (years)	0.0575	=0.6126
Gestational age (weeks)	0.146	=0.1973
Parity	-0.0311	=0.7841

rho: Spearman's rho (correlation coefficient).

After applying (Forward technique) and adding several predictor variables, a logarithmic regression analysis revealed that the rise in IUGR prevalence had a significant independent effect on the probability of occurrence of vitamin D deficiency, and a significant decrease in gestational age as an independent influence on raising the likelihood that vitamin D deficiency would occur (Table 6).

Table (6): Logistic regression model factors affecting occurrence of vitamin D deficiency using forward method

Predictor Factor	Coefficient	Std. Error	P value
(Constant)	7.66824		
Gestational age	-0.31626	0.14154	0.025*
IUGR	1.93131	0.59694	0.0012**

*: Significant, **: Highly significant

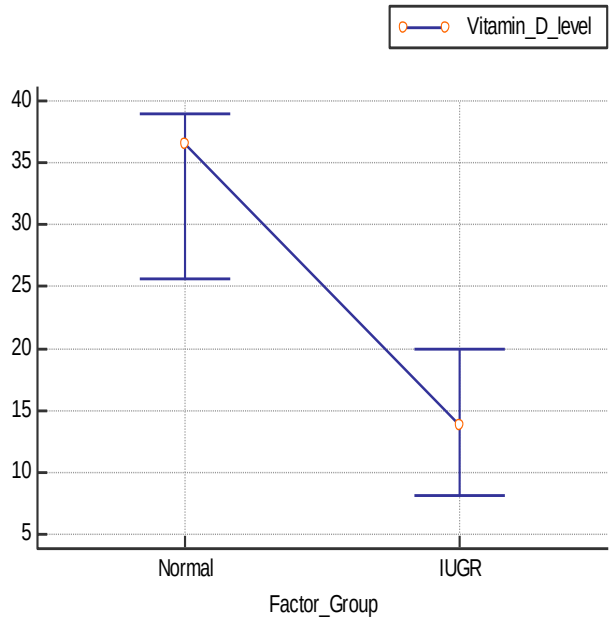

Figure (2): Correlation between vitamin D level IUGR

Vitamin D level at a cutoff point (28) predicted patients with IUGR with fair accuracy, sensitivity = 80%, specificity = 62.5%, using ROC-curve analysis. Age, gestational age, and parity did not have significant predictive values in patients with IUGR (Table 7).

Table (7): ROC-curve of some factors to predict patients with IUGR

Variable	AUC	SE	Best Cut off point (Criterion)	Sensitivity (%)	Specificity (%)	P value
Age	0.623	0.0634	≤27	72.50	52.50	0.0526
Gestational age	0.520	0.0649	≤29	37.50	72.50	0.7544
Parity	0.537	0.0624	>6	12.50	99	0.5479
Vitamin D level	0.750	0.0550	≤28	80	62.50	<0.0001**

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.

DISCUSSION

In our examination, vitamin D level was estimated by ELISA technique that separated it into deficiency as >10 ng/ml, inadequacy as10-30 ng/ml and adequacy as 30-100 ng/ml.

- **Group 1** showed: 47.5% (19 ladies) deficient, 32.5% (13 ladies) inadequate, and 20% (8 ladies) adequate.
- **Group 2** showed: 12.5% (5 ladies) deficient, 25% (10 ladies) inadequate, and 62.5% (25 ladies) adequate.

Also, we found that mean vitamin D level in all the patients was (24.6 ± 15) ng/ml. With respect to classes, (30%) patients had vitamin D deficiency, (28.7%) had vitamin.
D inadequacy, (41.2%) had adequate vitamin D.

Relative examination between 2 groups uncovered the following:

No significant difference was found as regards age and gestational age ($p > 0.05$). Also, there was highly huge decline in vitamin D level, in IUGR group, contrasted with ordinary group, with highly significant difference ($p = 0.00012$). Highly noteworthy increment in inadequate vitamin D class was found in IUGR group, contrasted with ordinary gathering, with highly significant difference ($p = 0.0002$).

Calculated relapse examination showed that; in the wake of applying (Forward strategy) entering some indicator factors revealed that: the decline in gestational age; independently affected expanding likelihood event vitamin D inadequacy; with critical measurable contrast ($p = 0.025$). The increment in IUGR pervasiveness; independently affected expanding likelihood event of vitamin D lack; with highly significant difference ($p = 0.0012$).

The present examination found a connection between intrauterine development impediment and maternal vitamin D insufficiency, which was profoundly huge. Our study is in an accordance with **Miliku *et al.*** [9] who found a positive connection between low maternal vitamin D levels during pregnancy with fetal growth restriction with expanded risk of preterm birth and small for gestational age during childbirth.

We also agree with **Ali *et al.*** [10] who stated that vitamin D supplementation decreases the chance of pre-eclampsia IUGR in a portion dependent way, this investigation was performed in King Fahad Medical City antenatal center from October 2012–October 2015, serum 25[OH]D broke down during first trimester (between 6-12 weeks pregnancy). Patients with vitamin D3 deficiency (serum levels 25 nmol/L) were included in the trial. vitamin D3 supplementation was randomised to 400 IU (Group 1) or 4000 IU (Group 2). The two groups were analyzed for predominance of pre-eclampsia portion impact on vitamin D level. 164 pregnant women were enrolled in the study .Mean maternal 25[OH]D basically increased from 16.3 $\pm$ 5 to 72.3 $\pm$ + 30.9 nmol/mL in group 2 and from 17.5 $\pm$ 6.7 to 35.3 $\pm$ 20.7 nmol/mL in group 1 ($p > 0.0001$). 4.3% of the study population had pre-eclampsia. Group 2 experienced fewer pre-eclampsia episodes over the trial period (8.6% versus 1.2%; $p< 0.05$) than group 1 did. In group 2 (9.6%) there were fewer IUGRs than in group 1 (22.2%).

Also, **Sarma *et al*.**[11] agreed with us that there is a positive relationship found between maternal hypovitaminosis D and shorted fetal femur length; this examination was completed on 250 solid primigravida (18-40 years of age) in third trimester growth (34 weeks) with singleton pregnancy who attended Obstetrics Gynecology Department, Gauhati Medical College, India from December 2012 to December 2015.They were assembled into group1 (150 moms) had low serum vitamin D levels, group2 (100 moms) had typical serum D levels.

A positive connection between maternal vitamin D insufficiency during pregnancy low birth weight was detected by **Khalessi *et al*.**[8] . This examination was done in nursery ward AliAsghar Akbarabadi Hospitals (Tehran-Iran) from January 2011 to January 2012, among 102 moms utilizing ELISA strategy (51 of them had low birth weight other 51 had ordinary birth weight) in the wake of barring all hazard factors that may influence birth weight other than vitamin D status. (48%) of moms had D inadequacy, (27.5%) had vitamin D deficiency (24.5%) had ordinary level. All moms' neonates with head circuit ≤ 33 cm likewise had vitamin D lack. This examination demonstrated that maternal

vitamin D inadequacy may expand chance of low birth weight neonate , so achieving normal maternal vitamin D level could have valuable effect on pregnancy outcome. Numerous examinations indicated significance of vitamin D supplementation during pregnancy and its advantages on neonatal results.

Surveying impact of maternal vitamin D supplementation prescribed by organization medication on neonatal vitamin D status with small for gestational age done by **Tao *et al.*** [12] as a section China–Anhui Birth Cohort study, maternal sociodemographic qualities, nourishment consumption, way of life, data on D supplementation, birth results were tentatively gathered. Included pregnant ladies received 600 IU/d D3 routinely during pregnancy. Cord blood levels of25(OH)D, calcium, and phosphorus were estimated in 1491 neonates who were partitioned into three gatherings dependent on term maternal vitamin D supplementation during pregnancy. Mean cord blood fixations, 25(OH)D 3.5 nmol/L, was higher in neonates whose mother took vitamin D supplementation >2 months during pregnancy contrasted and those whose mother didn't take any enhancement. Balanced hazard of SGA in pregnant ladies with vitamin D supplementation >2 months altogether diminished than that in ladies with no vitamin D supplementation. Along these lines, this examination propose that maternal vitamin D supplementation brings about a slight yet essentially higher fetal level 25(OH)D and improves fetal development.

All the above-mentioned studies agreed with us about the presence of significant relationship between FGR and maternal hypovitaminosis D, so every effort should be done to prevent this as often FGR is associated with consequences that raise maternal mortality and morbidity, such as hypertension, preeclampsia, eclampsia, and HELLP syndrome [13].

CONCLUSION

This study shows relationship between maternal vitamin D insufficiency and IUGR. Maternal vitamin D level ought to be estimated during pregnancy. Pregnant ladies ought to be urged to get normal sources of vitamin D, for example, satisfactory sun presentation and eating nourishment wealthy in vitamin D. RCOG proposals with respect to vitamin D supplementation ought to be satisfied.

ACKNOWLEDGMENTS

The patients who were enrolled in the study and Ain Shams University are both sincerely appreciated by the authors.

- **Funding:** No funding sources are available.
- **Conflict of interest:** No conflict of interest has been reported.

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