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The Relation between Vitamin D Deficiency and Fetal Growth Restriction in Pregnant Women

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ABSTRACT
Background: Fetal growth restriction represents pathological inhibition of fetal growth and failure of the fetus to attain its growth potential. There is a strong association between stillbirth and fetal growth restriction.
Objective: The aim of this study was to detect the relationship between Vitamin D deficiency in pregnancy and intrauterine growth restriction (IUGR).
Patients and method: This case control study included a total of 56 pregnant women, attending for antenatal care at Department of Obstetrics and Gynecology, Faculty of Medicine, Maternity Hospital, Zagazig University. The included subjects were divided into two equal groups: **Case Group (**fetal growth restriction**)** and **Control Group (**healthy**)**. Vitamin D level was measured at 35 weeks of gestational age by electrochemiluminescence technique.
Result: All control group regularly consumed dairy products versus 78.6% within case group and 96% within control group versus 60.7% within case group receive calcium supplementation. regarding serum vitamin D level, it was significantly lower in case group than control group. Very severe vitamin D deficiency level (< 5 ng/ml) occurred in 10.7% within case group versus 3.6% in control group while sever vitamin D deficiency (5-10) occurred in 50% in case group and 35.7% in control group while suboptimal level (20-30) in 14.3% case group and 25% in control group, optimal level prevailed (30-50) in 3.6% and 14.3% within case and control groups respectively. The best cutoff value of serum vitamin D in prediction of IUGR was considered as <11.5ng/dl with area under curve 0.667, sensitivity 75%, specificity 53.6%, positive predictive value 61.8%, negative predictive value 68.2% and overall accuracy 64.3% (p<0.05).
Conclusion: It could be concluded that vitamin D deficiency could be a risk factor for the occurrence of fetal growth restriction.
Keywords: Vitamin D, Fetal Growth, Pregnant Women

INTRODUCTION
Intrauterine growth restriction that commonly occurs in intrauterine environments insufficiency increases mortality and morbidities for the rest of life by five to ten times [(1)].

There is a link between perinatal morbidity and death with intrauterine growth restriction. IUGR was defined by the American College of Obstetricians and Gynecologists as the percentage of fetal growth that is less than normal given the growth potential of that particular newborn. Intrauterine growth restriction is a complex issue that affects both term and preterm babies. It increases the risk of preterm fatalities, acidemia, hypoxemia, and discomfort in the mother. Additionally, it increases the baby's risk of developing cerebral palsy, cognitive impairment, lung problems, intraventricular hemorrhage, polycythemia, and various metabolic diseases [(1, 2)]. Intrauterine growth limitation can occur for a number of reasons, among them are the past medical records of persistent maternal conditions (e.g., hypertension, kidney illnesses, diabetes, anemia, etc.), pregnancy weight increase, pregnancy age, pregnancy occupation, chromosomal abnormalities and various fetal infections, birth rank, interval between deliveries, neonatal sex, placental abruption and placenta previa [(2)].

This study aimed to assess the relationship between fetal development and growth and the mother's vitamin D status. This could serve as a foundation for maternal hypovitaminosis D prevention and treatment.

PATIENT AND METHODS
This case control research comprised 56 pregnant women who were getting prenatal treatment at Department of Obstetrics and Gynecology, Faculty of Medicine, Maternity Hospital, Zagazig University.

Two equal groups were created from the included subjects: the Case Group (fetal growth limitation) included 28 pregnant women, and **Control Group (**healthy**)** consisted of 28 healthy pregnant women.

Ethical consent:

The Research Ethics Committee of Zagazig University gave its ethical approval to this work, which was then submitted to Zagazig University (ZU-IRB# 9409). We obtained each participant's informed consent in writing. The study's protocol adhered to the World Medical Association's ethical guidelines for using human subjects in research, known as the Helsinki Declaration.

Inclusion criteria: Women who accepted to participate in the study, aged above 18 years, women with viable, single fetus, gestational age (28-39 weeks) and women with fetal growth restriction.
Exclusion criteria: non-viable fetus, multiple pregnancies, fetal congenital anomaly, women with any chronic conditions include high blood pressure, diabetes, kidney and heart problems, as well as women who declined to take part in the research.

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Every participant underwent a comprehensive clinical examination and had their whole medical history reviewed.

The measurement of Symphysial Fundal Height (SFH) was made from the highest uterine fundus to the superior boundary of the symphysis. One hand was used to wrap the tape over the upper boundary of the pubis symphysis bone. The tape was then placed over the uterus in a straight line until it reached the fundus and there was no more resistance felt. To record the value to the closest whole centimeter, the tape was spun such that the numerals were visible. After 30 weeks, abdominal circumference was measured at the umbilicus [(3)]. Serial ultrasound measurement in antenatal visits included femur length (FL), head circumference (HC), abdominal circumference (AC), and biparital diameter (BPD) in order to get the predicted fetal body weight. Ultrasonography was used to diagnose IUGR when the estimated fetal weight (EFW) was less than the 10th percentilefor gestational age[(4)].

Doppler examination:

Umbilical Artery Doppler (UA) The spectral Doppler indices in fetal growth restriction measured at the placental end, the free loop, and the end of the umbilical cord that is fetal. The blood velocity waveform in the umbilical cord artery typically varies gradually as seen below: Decreasing end-diastolic flow can be achieved via raising RI, PI, and S/D ratios as well as by reversing or absent end-diastolic flow (AEDF) (REDF) [(5)]. The Middle cerebral artery Doppler (MCA) was identified overlying the front wing of the sphenoid bone close to the base of the skull in the transverse plane of the fetal head at the obvious passage point into the Circle of Willis, diminished Pulsatility index (Pl) and Systolic/Diastolic (S/D) proportion in considered abnormality [(6)].

Ductus venosus Doppler examination (DV) was found in a growth-restricted fetus at risk for late circulatory alterations linked to fetal deterioration and decompensation using color Doppler imaging in an oblique or sagittal perspective. The large rise in placental afterload in this scenario, coupled with myocardial hypoxia-related aberrant DV Doppler and loss of biophysical factors ranging from 1 to 8 days, can result in an irregular DV waveform. It is improbable that a fetus will survive for more than a week when the DV forward a-wave is absent or inverted [(5)].

Investigations including The Complete Blood Count (CBC), coagulation profile, liver, kidney, and thyroid functions, blood glucose level, and urine albumin level are used to rule out pre-eclampsia.

Vitamin D Measurement:

A Serum total 25(OH) vitamin D3 was measured at (35±2) week gestation by electrochemiluminescence technique. After drawing blood samples, sera was isolated and kept cold (-80°C) until further examination. The electrochemiluminescence analyzer Roche E601 was utilized.

Statistical analysis

Data entry, processing, and statistical analysis were performed using MedCalc version 18.2.1 (MedCalc, Ostend, Belgium). Use the Chi square test (x2) to ascertain the difference between two or more sets of qualitative variables. Quantitative data was expressed as mean±SD or standard deviation (SD). The independent samples t-test was used to compare two independent groups of normally distributed variables (parametric data). The ROC Curve analysis, Mann-Whitney's, Chi square, logistic and multiple regression analysis, Spearman's correlation, and other important tests were used. After the data were presented, a pertinent analysis was carried out depending on the kind of data (parametric and non-parametric) obtained for each variable. P-values were deemed statistically significant if they were 5% or less.

RESULT

Table 1 shows that there were statistically **significant** differences between the studied groups regarding age and occupation. Case group subjects were significantly younger (25.29 ± 4.55, years) than control group (28.25 ± 4.62, years). Larger percentage of women with fetuses had IUGR were housewives (89.3%) versus 46.4% within control group.

Table (1): Comparison between the studied groups regarding demographic data:

Parameter	Groups		Test	
	Case group N=28 (%)	Control group N=28 (%)	t/x^2	P
Age (year): Mean ± SD	25.29 ± 4.55	28.25 ± 4.62	2.417	0.019*
BMI (kg/m^2): Mean ± SD	28.57 ± 6.87	30.51 ± 5.53	1.162	0.25
Occupation: Housewife/student Unskilled worker Skilled worker	25 (89.3%) 0 (0%) 0 (0%) 3 (10.7%)	13 (46.4%) 1 (3.6%) 2 (7.1%) 12 (42.9%)	10.122§	0.001**
Special habits: No	28 (100%)	28 (100%)	Fisher	>0.999

X^2Chi square test §chi square for trend test t independent sample t test *p<0.05 is statistically significant **p<0.001 is statistically highly significant

Table 2 shows that there was statistically **significant** difference between the studied groups regarding using dairy products and calcium supplementation. All control group regularly consumed dairy products versus 78.6% within case group. About 96% within control group versus 60.7% within case group received calcium supplementation. There was statistically non-significant difference between the studied groups regarding use of vitamin D supplementation.

Table (2): Comparison between the studied groups regarding dietary data

Parameter	Groups		Test	
	Case group N=28 (%)	**Control group N=28 (%)**	**x^2**	**P**
Dairy products consumption Yes No	 22 (78.6%) 6 (21.4%)	 28 (100%) 0 (0%)	Fisher	0.023*
Vitamin D supplement No	 28 (100%)	 28 (100%)	Fisher	>0.999
Calcium supplementation: Yes No	 17 (60.7%) 11 (39.3%)	 27 (96.4%) 1 (3.6%)	10.606	0.001**

X^2Chi square test *p<0.05 is statistically significant **p<0.001 is statistically highly significant

Table 3 shows that there was statistically **significant** difference between the studied groups regarding hemoglobin level which was significantly lower in case group. There was statistically non-significant difference between the studied groups regarding presence of albuminuria.

Table (3): Comparison between the studied groups regarding laboratory data at Gestational age (35.61 ± 2)

Parameter	Groups		Test	
	Case group N=28	**Control group N=28**	**T**	**P**
Hemoglobin (g/dl): Mean ± SD	8.05 ± 1.1	9.64 ± 1.04	2.063	0.044*
Albuminuria: Negative	28 (100%)	28 (100%)	Fisher	>0.999

t independent sample t test *p<0.05 is statistically significant **p<0.001 is statistically highly significant

Table 4 shows that there were statistically significant differences between the studied groups regarding ultrasonographic parameters (biparietal diameter, abdominal circumference, femur length, amniotic fluid index) where all were significantly lower in case group at Gestational age=35w. There was statistically significant difference between the studied groups regarding estimated fetal weight which is significantly lower in case group**.**

Table (4): Comparison between the studied groups regarding ultrasonographic fetal parameters at Gestational age (35.61±2 weeks)

Parameter	Groups		Test	
	Case group N=28 (%)	**Control group N=28 (%)**	**t**	**P**
	Mean ± SD	**Mean ± SD**		
BPD	30.75 ± 2.65	35.43 ± 2.96	6.232	<0.001**
AC	30.39 ± 2.85	35.11 ± 2.86	6.184	<0.001**
FL	30.64 ± 2.83	35.39 ± 2.94	6.163	<0.001**
AFI	8.43 ± 2.01	12.82 ± 2.44	7.635	<0.001**
Estimated fetal weight	1622.89 ± 401.21	2224.18 ± 474.37	5.038	<0.001**

t independent sample t test **p<0.001 is statistically highly significant * BPD biparital diameter AC Abdominal circumflex*FL Femoral length*AFI Amniotic fluid index

Table5 :shows that the resistance index in umbilical artery **UA (RI**) was significantly higher in case group than control group. The resistance index in middle cerebral artery **MCA(RI)** was significantly lower in case group. The pulsatility index in umbilical artery **UA (PI**) was significantly higher in case group than control group. The pulsatility index in middle cerebral artery **MCA (PI**) was significantly lower in case group. There was no significant difference between systolic/diastolic ratio in umbilical artery **UA (S/D)** between case group and control group. There were no significant difference between systolic/diastolic ratio in middle cerebral artery MCA **(S/D)** between case group and control group.

Table (5): Comparison between the studied groups regarding Doppler parameters at Gestational age (35.61 ± 2)

Parameter	**Groups**		**Test**	
	Case group N=28 (%)	**Control group N=28 (%)**	**Z**	**P**
UA (RI): Median (IQR) Range	0.91 (0.81 - 0.95) 0.71 - 0.93	0.22(0.165-0.475) 0.1-0.7	4.486	0.0001**
MCA (RI) Median (IQR) Range	0.47(0.32-0.58) 0.2-0.73	0.63(0.44-0.82) 0.42-0.91	4.023	0.0001**
UA (PI): Median (IQR) Range	1.45(0.98-1.5) 0.7-1.8	0.5(0.4-0.7) 0.3-0.9	6.192	0.0001**
MCA (PI) Median (IQR) Range	1.3(1.2-1.675) 0.4-1.8	1.6(1.4-1.87) 1.3-1.9	5.094	0.0001**
UA (S/D): Median (IQR) Range	3.12(2.88-3.13) 2.78-3.7	3.35(3.19-3.47) 3.11-3.7	4.805	0.0001**
MCA (S/D) Median (IQR) Range	2.94(2.83-3.16) 2.22-3.7	3.33(3.19-3.47) 3.11-3.7	4.558	0.0001**

Z Mann Whitney test **p<0.001 is statistically highly significant, IQR interquartile range

Table 6 shows that There was statistically significant difference between the studied groups regarding serum vitamin D level (ng/ml) which was significantly lower in case group. Very severe vitamin D deficiency level (<5) occurred in 10.7% within case group versus 3.6% in control group while optimal level prevailed (30-50) in 3.6% and 14.3% within case and control groups respectively.

Table (6): Comparison between the studied groups regarding and vitamin D level done at Gestational age (35.61 ± 2) weeks.

Parameter	**Groups**		**Test**	
	Case group N=28 (%)	**Control group N=28 (%)**	**t**	**P**
Vitamin D: ng/ml Mean±SD IQR Range	 8.31±1.71 6.35 - 14.15 4.2 - 35	 11.9±2.41 8.11 - 24.88 4.72 - 37	2.227	0.023*
Very severe deficiency (<5) **Severe deficiency (5-10)** **Vitamin D deficiency** (**10-20**) **Suboptimal level** (**20-30)** **Optimal Vitamin D (30-50)**	3 (10.7%) 14 (50%) 6 (21.4%) 4 (14.3%) 1 (3.6%)	1 (3.6%) 10 (35.7%) 6 (21.4%) 7 (25%) 4 (14.3%)	4.123	0.042*

X2Chi square for trend test Z Mann Whitney test *p<0.05 is statistically significant IQR interquartile range

In case group, there was statistically **significant** positive correlation between serum vitamin D and Biparietal diameter, abdominal circumference. There was no significant correlation between serum vitamin D and either femur length or amniotic fluid index. In control group, there was no significant correlation between serum vitamin D and either Biparietal diameter, abdominal circumference, femur length or amniotic fluid index. In case group. There was statistically **significant** positive correlation between serum vitamin D and estimated fetal weight. In control group. There was no significant correlation between serum vitamin D and estimated fetal weight (Table 7).

Table (7): Correlation between vitamin D and ultrasonographic data in Case group and control group at (35.61 ± 2)

Variables	VIT D level of case group		VIT D level of control group	
	R	P	R	P
BPD	**0.379**	**0.051**	0.174	0.376
AC	**0.376**	**0.049**	0.186	0.343
FL	0.309	0.109	0.149	0.448
AFI	0.042	0.834	-.040	0.84
EFBW	**0.416***	**0.028**	0.28	0.148

r Spearman rank correlation coefficient *p<0.05 is statistically significant

Regarding umbilical artery, in case group, there was significant negative correlation between serum vitamin D level and resistance and pulsatility index, on the other hand, there was no significant correlation between serum vitamin D level and systolic/diastolic ratio in both case and control groups. Regarding middle cerebral artery, in case group, there was statistically significant positive correlation between serum vitamin D level and resistance and pulsatility index, on the other hand, there was no significant correlation between serum vitamin D level and systolic/ diastolic ratio in both case and control groups (Table 8).

Table (8): Correlation between vitamin D and doppler parameters in Case group and control group in Gestational age (35.61±2)

Variables	VIT D level of case group		VIT D level of control group	
	R	P	R	P
UA(RI)	-0.217	0.028	0.041	0.835
UA(PI)	-0.022	0.091	0.005	0.980
UA(S/D)	0.028	0. 72	0. 01	0.621
MCA(RI)	0.452	0.016	0.053	0.789
MCA(PI)	0.153	0.043	0.05	0.81
MCA(S/D)	0.102	0.605	0. 08	0.062

r Spearman rank correlation coefficient *p<0.05 is statistically significant

Figure 1: The best cutoff value of serum vitamin D in prediction in prediction of IUGR is<11.5 ng/dl with area under curve 0.667, sensitivity 75%, specificity 53.6%, positive predictive value 61.8%, negative predictive value 68.2% and overall accuracy 64.3% (p<0.05).

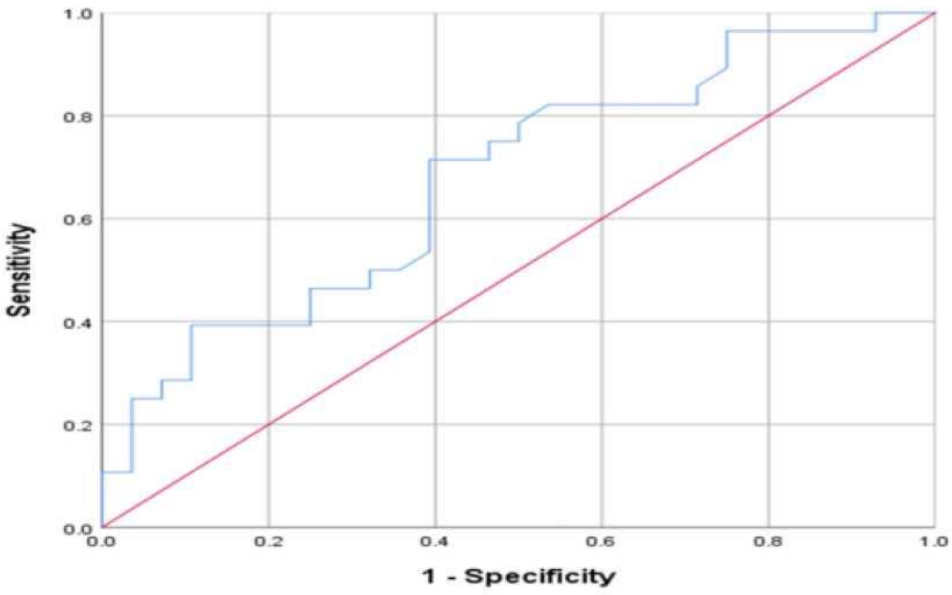

Figure (1): ROC curve showing performance of serum vitamin D in prediction of IUGR among studied participants.

DISCUSSION

This study reported that women in IUGR group were statistically significantly younger (25.29±4.55 years), and the proportion of housewives was greater than that of the healthy group. But there was no difference in the two groups' body mass indices (28.57±6.87) kg/m^2.

Mohammad *et al.*[8] concurred with our research and said that a lower mother's age (25.8± 2.1 years) is a risk factor for IUGR. Following the multivariable model's confounder correction, their case-control study revealed that the maternal factors associated with IUGR were younger age (OR=0.9, CI=0.8-0.9), body mass index, and (25.74±3.8) kg/m^2 (OR=3.0, CI=1.6-6.1)

This study reported that all women in control group regularly consumed dairy products and calcium supplementations higher than cases in IUGR collective. However, none of the ladies in either group took supplements containing vitamin D.

In agreement with our study, **Che *et al. (9)*** showed that placental lipid and energy metabolism were primarily modulated by inadequate maternal nutrition, which also offers a potential explanation for the higher fetal weight uniformity in gilts fed a low-energy diet.

Yang *et al.* [10] also agreed with us and stated that increased dietary protein intake especially from animal sources and dairy products is linked to lower chances of LBW, SGA, and IUGR as well as greater birth weight.

Current study reported that in case group; Serum vitamin D exhibited a statistically significant positive connection with estimated fetal weight, abdominal circumference, and biparietal diameter. which concurs with **Tao *et al.***[11] who had stated that inadequate or lacking in vitamin D would dramatically impact the fetal bone's growth and development during pregnancy, influencing the head and stomach circumferences and raising the likelihood of an SGA birth. When compared The mother who took vitamin D supplements for more than two months had a significantly decreased incidence of SGA compared to expectant mothers who did not take any supplements. (11.8%vs 6.9%) Disagreeing with, **Eggemoen *et al.***[12] who stated that No significant correlation was found among the neonatal anthropometric measurements and the maternal vitamin D levels in a multiethnic population of expecting mothers with a high frequency of vitamin D deficiency (P <0-05).

In the current study, the estimated fetal weight which was considerably lower in the case group that concurred with **Khalessi *et al.***[13] who asserted that a mother's deficiency in vitamin D may increase the likelihood that her child may be born underweight. The mean maternal vitamin D level for LBW babies was 25.05 vs. 38.13 (p = 0.001), which was lower than the other group. Every mother of an infant with a head circumference under 33 cm also had a vitamin D deficiency (p = 0.007).

Regarding Doppler parameters; our study reported that all indices were negatively When comparing the IUGR group to the healthy group, there was an impact on the correlation between serum vitamin D level and pulsatility index and umbilical artery resistance. Additionally, there was a positive correlation between vitamin D level and middle cerebral artery resistance as well as pulsatility index in the IUGR group.

Jakubiec-Wisniewska *et al.*[14] claimed that the rise in the cerebroplacental ratio (CPR) in fetuses with early FGR was influenced by vitamin D treatment at a dose of 2000 IU. A prospective cohort study was conducted. The groups of pregnant women were supplemented with vitamin D at a dose of less than 500 IU and 2000 IU, respectively. The two groups were watched for seven and fourteen days. A statistically significant variation was observed in the absolute CPR values (p = 0.0032). The fetuses of patients getting 2000 IU of vitamin D (1.75 vs. 1.55) group receiving vitamin D at a dose<500 IU, according to measurements made on the seventh day of observation. In the same way, on day 14: (p< 0.0001) (2.39 vs 1.21).

This study reported that serum vitamin D level was significantly lower in IUGR group. Sever vitamin D deficiency level (<5 ng/ml) occurred in 10.7% of cases Roc Curve analysis of vitamin D showed that cut off value of serum vitamin D prediction of IUGR was < 11.5 ng/dl with area under curve 0.667 had sensitivity of 75%, specificity of 53.6%, positive predictive value of 61.8%, negative predictive value of 68.2% and o accuracy of 64.3% (p<0.05) in detecting IUGR.

Alimohamadi *et al.* [2] established that serum Since vitamin D levels can affect IUGR risk, babies whose moms received enough of it during pregnancy are less likely to experience IUGR than babies whose mothers did not. The average serum vitamin D levels in the case and control groups were around 14.74 ng/L and 25.34 ng/L, respectively. Women with inadequate amounts of vitamin D were nearly six times more likely to experience IUGR than women with normal levels of the vitamin. (P <0.05).

Zhao *et al.*[15] disagreed with current study as they proved that a sufficient vitamin D status during pregnancy not associated with IUGR. Databases includes Web of Science, Embase, PubMed, and Scopus for observational studies with the following criteria: case-cohort, cohort, or nested case-control studies. This systematic review contained 72 publications in total, yet there were 71 publications in the meta-analysis. In the highest versus lowest meta-analysis, the concentrations of 25(OH)D in mothers were inversely correlated with the risk of LBW (RR: 0.65; 95% CI 0.48-0.86), PTB (RR: 0.67; 95% CI 0.57-0.79), and SGA (RR: 0.61; 95% CI 0.49-0.76), but not with Macrosomia (MA) or intrauterine growth restriction (IUGR).

CONCLUSION

It could be concluded that fetal development restriction may arise as a result of a vitamin D shortage.

RECOMMENDATIONS

Exposure to sun light It is crucial to know which is the primary source of vitamin D throughout a given day. Every lady needs to address her vitamin deficiencies before conception. Early pregnancy 25(OH)D3 assessment is advised.

The incidence of IUGR and the fetus's neonatal morbidity and death may be reduced by taking vitamin D supplements prior to, throughout, and after pregnancy. Research ought to keep up the efficacy of supplementation and its possible side effects on mothers during pregnancy.

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