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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 ≤11.5 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% ($p<0.05$).

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 is a prevalent disease in pregnancy in which placental insufficiency leads to 5 to 10 times higher mortality and lifelong morbidities [(1)].

Intrauterine growth restriction is associated with prenatal mortality and morbidity. A satisfactory definition of IUGR has been the rate of fetal growth that is less than normal considering growth potential of that specific infant suggested by the American College of Obstetricians and Gynecologists. Intrauterine growth restriction is a multifaceted problem, that increases the risk of hypoxemia, acidemia, preterm deaths, and maternal distress, and disposes the infant to several metabolic disorders, polycythemia, lung problems, intraventricular hemorrhage, cognitive dysfunction, and cerebral palsy, which occur in both term and preterm infants [(1, 2)]. Some of the effective factors for the occurrence of intrauterine growth restriction include the history of chronic maternal diseases (high blood pressure, renal diseases, diabetes, anemia, etc.) maternal weight gain during pregnancy, maternal age during pregnancy, occupation, different types of fetal infections and chromosomal abnormalities, birth rank, delivery interval, neonatal sex, placental abruption, and placenta previa [(2)].

The aim of this study was to evaluate the relationship between maternal vitamin D status and fetal growth and development. This may provide a basis for the prevention and intervention of maternal hypovitaminosis D.

PATIENT AND METHODS

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**)** consisted of 28 pregnant women, and **Control Group (**healthy**)** consisted of 28 pregnant women.

Ethical consent:

This study was ethically approved by Zagazig University's Research Ethics Committee, and submitted them to Zagazig University (ZU-IRB# 9409). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

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 diseases such as hypertension, diabetes mellitus, cardiac disease and renal disease and women who did not accept to participate in the study.

All participants were subjected to full detailed medical history and thorough clinical examination.

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Symphysial Fundal Height (SFH) was measure from the superior border of the symphysis to the highest uterine fundus. The tape was positioned with one hand over the upper border of the pubis symphysis bone, and the tape was placed in a straight line over the uterus until loss of resistance was felt when reaching the fundus. The tape was turned so that the numbers were visible to record the value to the nearest complete one centimetre. Abdominal girth was measured at the level of umbilicus beyond 30 weeks [(3)]. Serial ultrasound measurement in antenatal visits included head circumference (HC) Biparital diameter (BPD), abdominal circumference (AC) and femoral length (FL) to detect estimated fetal body weight. for diagnosing IUGR was by ultrasound the estimation fetal weight (EFW) below the 10^{th} percentile) [(4)] for gestational age.

Doppler examination:

Umbilical Artery Doppler (UA) The spectral Doppler indices measured at the fetal end, the free loop, and the placental end of the umbilical cord in fetal growth restriction. The umbilical artery blood velocity waveform usually changes in a progressive manner as below; Reduction in end-diastolic flow: increasing RI values, PI values, and S/D ratio and absent end-diastolic flow (AEDF) or reversal of end-diastolic flow (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 identified with color Doppler in a sagittal or oblique view in growth restricted fetus at risk for late cardiovascular changes associated with fetal deterioration and decompensation. In this setting, an abnormal DV waveform can occur as a result of the massive increase in placental afterload, decreased myocardial performance and compliance due to myocardial hypoxia abnormal DV Doppler and loss of biophysical variables ranges between 1 and 8 days. When DV forward a-wave is absent or reversed, fetal survival of longer than 1 week is unlikely [(5)].

Investigations including Complete Blood Count (CBC), coagulation profile, liver function tests, Renal function tests, thyroid function tests, and blood glucose level, urine for albumin to exclude pre-eclampsia.

Vitamin D Measurement:
A Serum total 25(OH) vitamin D3 was measured at (35±2) week gestation by electrochemiluminescence technique. Blood samples were taken, and sera was separated and stored at –80°C until analysis. Roche E601 electrochemiluminescence analyzer was used.

Statistical analysis

Data entry, processing and statistical analysis was carried out using MedCalc ver. 18.2.1 (MedCalc, Ostend, Belgium). Chi square test ($\chi2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). Tests of significance (Mann-Whitney's, Chi square, logistic and multiple regression analysis, Spearman's correlation, and ROC Curve analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was statistically significant.

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/χ^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:			$10.122^§$	0.001**
Housewife/student	25 (89.3%)	13 (46.4%)		
Unskilled worker	0 (0%)	1 (3.6%)		
Skilled worker	0 (0%)	2 (7.1%)		
Employee	3 (10.7%)	12 (42.9%)		
Special habits:			Fisher	>0.999
No	28 (100%)	28 (100%)		

χ^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 (%)	χ^2	P
Dairy products consumption				
Yes	22 (78.6%)	28 (100%)	Fisher	0.023*
No	6 (21.4%)	0 (0%)		
Vitamin D supplement			Fisher	>0.999
No	28 (100%)	28 (100%)		
Calcium supplementation:				
Yes	17 (60.7%)	27 (96.4%)	10.606	0.001**
No	11 (39.3%)	1 (3.6%)		

χ^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

Table 5 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*

χ^2Chi 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).

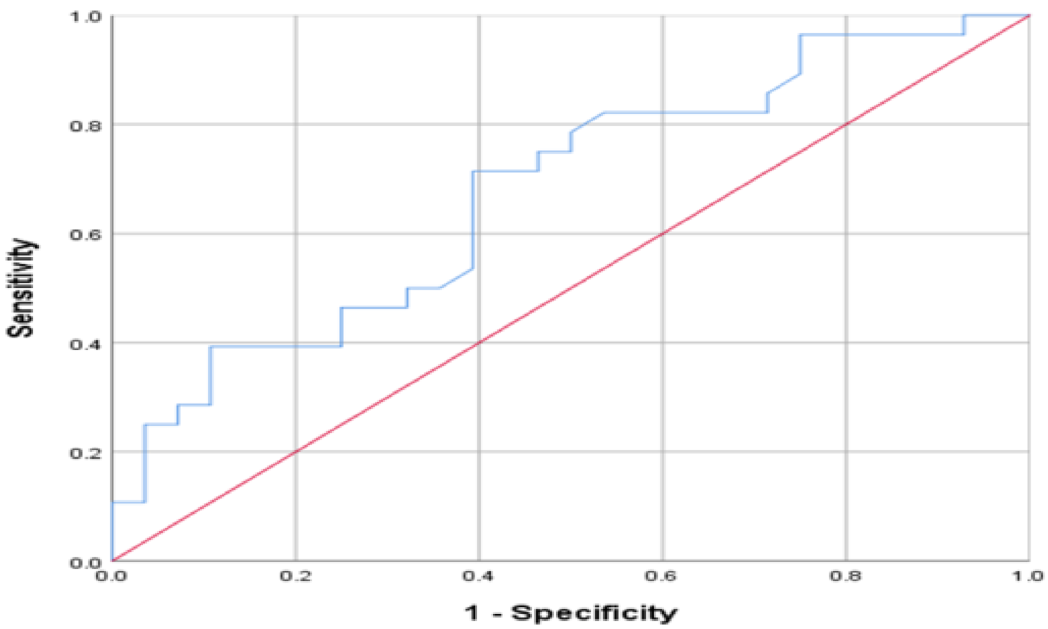

Figure (1): ROC curve showing performance of serum vitamin D in prediction of IUGR among studied participants.

DISCUSSION

This study reported that women in IUGR group were statistically significantly younger (25.29±4.55 years), and percent of housewives was higher compared with healthy group._On the other hand, there was no difference between both groups regarding body mass index (28.57 ± 6.87) kg/m^2.

Mohammad *et al.*[8] agreed with our study and stated that younger (25.8± 2.1 years), maternal age is a risk factor of IUGR. Their case-control study reported that maternal factors associated with IUGR after adjusting for confounders in the multivariable model included younger age (OR=0.9, CI=0.8-0.9), body mass index (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 group. On the other hand, no women in both groups used vitamin D supplementation.

In agreement with our study, **Che *et al.*** [9] revealed that poor maternal nutrition altered birth weight mainly through the modulation of placental lipid and energy metabolism, which also provides a possible mechanism to explain the higher uniformity of fetal weight in gilts fed a low energy diet.

Yang *et al.* [10] also agreed with us and stated that higher intake of dietary protein, in particular animal protein and dairy product, is associated with higher birth weight and lower risks of LBW, SGA, and IUGR.

Current study reported that in case group; there was statistically significant positive correlation between serum vitamin D and biparietal diameter, abdominal circumference and estimated fetal weight. Which is in agreement with **Tao *et al.*** [11] who had reported that vitamin D deficiency/ Insufficiency during pregnancy would seriously affect the growth and development of fetal bones, thereby affecting the abdominal circumference, head circumference, greatly increasing the birth probability of SGA. The pregnant mother took vitamin D supplementation for >2 months decreased significantly the risk of SGA compared with pregnant mother without any vitamin D supplementation (11.8% vs 6.9%) Disagreeing with, **Eggemoen *et al.*** [12] who stated that in a multiethnic cohort of pregnant women with high prevalence of vitamin D deficiency, no independent relation between maternal vitamin D levels and any of the neonatal anthropometric measures (P <0·05).

In the current study, the estimated fetal weight which was significantly lower in case group agreed with **Khalessi *et al.***[13] who stated that maternal Vitamin D deficiency may increase the risk of low birth weight neonate. Mean maternal vitamin D level of LBW neonates was lower than other group; 25.05 vs. 38.13 (p = 0.001). All mothers of neonates with head circumference ≤ 33 cm also had vitamin D deficiency (p = 0.007).

Regarding Doppler parameters; our study reported that all indices were negatively correlation between serum vitamin D level and umbilical arteries resistance and pulsatility index, was affected in group of IUGR compared with healthy group , and there were a positive correlation between vitamin D level and middle cerebral artery resistance , and pulsatility index in group of IUGR compared with healthy group.

Jakubiec-Wisniewska *et al.*[14] stated that supplementation with vitamin D at a dose of 2000 IU had an influence on the increase in the cerebroplacental ratio (CPR) in fetuses with early FGR. It was a prospective cohort study. Pregnant females were divided into groups with vitamin D supplement <500 IU and other group with vitamin D supplement 2000 IU. Both groups were observed for 7 days and14 day Absolute CPR values were significantly different (p = 0.0032). Measurements on the seventh day of observation indicated that CPR was significantly higher (p = 0.0455) in fetuses of patients receiving vitamin D at a dose of 2000 IU (1.75 vs. 1.55) group receiving vitamin D at a dose<500 IU Similarly, 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] concluded that the serum levels of vitamin D can affect the risk of IUGR; therefore, the incidence of IUGR in babies whose mothers have enough vitamin D level during pregnancy is lower than that in other babies. Average serum levels of vitamin D were about 14.74 ng/L and 25.34 ng/L in the case and control groups, respectively. Women who had vitamin D deficiency, had almost 6 times more chance of IUGR compared to the women with adequate levels of vitamin D (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 including PubMed, Embase, Scopus, and Web of Science for observational studies that fulfilled criteria as follows: cohort studies, case–cohort studies, or nested case–control studies. A total of 72 publications were included in this systematic review and 71 in the meta-analysis. Maternal 25-hydroxyvitamin D (25(OH)D) concentrations were inversely associated 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) in the highest versus lowest meta-analysis, but not associated with Macrosomia (MA) and intrauterine growth restriction (IUGR).

CONCLUSION

It could be concluded that vitamin D deficiency could be a risk factor for the occurrence of fetal growth restriction.

RECOMMENDATIONS

Exposure to sun light which is the main source of vitamin D in specific day time is very important. Every woman should correct vitamin deficiency before conception. Early pregnancy 25(OH)D3 assessment is advised.

The use of vitamin D supplement before, during and after pregnancy could be useful in decreasing the incidence of IUGR and decrease neonatal morbidity and mortality of the fetus. Research should continue the effectiveness of supplementation and its possible side effects on mothers during pregnancy.

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