



Early Uterine Perfusion Assessment in Selected Population with Hypovitaminosis D3: Which Factor is Predictive for Poor Pregnancy Outcome?

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Abstract

Objective: To assess uterine perfusion early in pregnancy in women with hypovitaminosis D3 and evaluate if findings are linked to poor pregnancy outcomes.

Patients and Methods: 300 primigravidae with singleton pregnancy (11weeks to13weeks) were included in this study attending for routine antenatal care at Tanta University Hospitals. Vitamin D3 levels were estimated plus transvaginal color Doppler ultrasound to measure the pulsatility index of the uterine arteries and the spiral arteries.

Results: The mean age of enrolled patients was 26.2±4.593 years, mean BMI was 27.64 ± 3.348 and the mean gestational age at booking was 8.54±1.72 weeks. Hundred and fourteen cases out of 300 cases (38%) had hypovitaminosis D3. The cases with hypoperfusion (43 cases) were complicated by spontaneous abortion (3 cases), preterm labor (4 cases), IUFD (4 cases), hypertension (17 cases), IUGR (7 cases), placental abruption (2 cases). Cases with hypovitaminosis only and normal perfusion were not linked to poor outcomes where only 3 cases suffered late preterm labour after 34 weeks with good neonatal outcomes.

Conclusion: Early uterine hypoperfusion in hypovitaminosis D3 had positive predictive factor in relation to poor pregnancy outcomes while deficiency of Vitamin D only was not related to poor pregnancy outcomes.

Keywords: Uterine artery doppler; Uterine perfusion; Vitamin D3; Pregnancy outcome

Introduction

Screening for adverse pregnancy outcomes should start early in the first trimester of pregnancy and is considered the most helpful method to detect any prenatal hazards. Many prenatal conditions could be detected if good screening was done appropriately in the first trimester. Feto-maternal conditions like Preeclampsia, preterm labor, gestational diabetes, as well as fetal growth restriction could easily be screened for in the first trimester [1].

Several biomarkers were screened for their relation to pregnancy outcome such as β-HCG, reactive oxygen species, fetal hemoglobin, α1-microglobulin and hemopexin, Soluble endoglin (sEng), serum copeptin and procalcitonin, CA125, E2 and Progesterone, Lactate Dehydrogenase (LDH), antinuclear antibodies (ANAs) and anti phospholipid antibodies (APAs), metalloprotease 12 (ADAM-12) and inhibin-A, pregnancy associated plasma protein A (PAPP-A), placental growth factor (PIGF) and placental protein 13 (PP-13) [2-11].

On the other hand, several ultrasonographic markers were proposed for screening of poor pregnancy outcome [12]. These include uterine artery Doppler, endometrial thickness, CRL, subchorionic hematoma, yolk sac diameter, and mean sac diameter, fetal heart rate abnormalities [2,13-17]. Uterine artery Doppler specifically was tested on a large scale by many researchers [18-22]. Doppler ultrasound provides a non-invasive method for the assessment of the uteroplacental circulation. Some studies found that impaired placental perfusion- reflected in increased uterine artery Pulsatility index (PI) and Resistive index (RI)-is associated with poor pregnancy outcome due to impaired placentation [23-26] while other studies stated that uterine artery Doppler done early in the first trimester with a living embryo is not helpful for predicting pregnancy outcome [27].

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Table 1: Demographic data of enrolled patients.

	Range	Mean ± SD
Age (years)	18.2-31.4	26.2 ± 4.593
BMI	21.70-33.09	27.64 ± 3.348
Gestational age at booking (weeks)	11-13	11.54 ± 1.72

The growing evidence nowadays supports the predictive value of Vitamin D3 in prediction of poor pregnancy outcome. The prevalence of vitamin D deficiency ranges from 22.7% to 90.3% [28,29]. A meta-analysis of observational studies has demonstrated positive association between vitamin D status and adverse pregnancy outcomes such as preeclampsia, gestational diabetes mellitus, preterm birth and small-for-gestational age. Vitamin D supplementation during pregnancy optimized maternal and neonatal outcomes [30- 33].

Although there is no consensus on an optimal level to maintain overall health, the Endocrine Society defined vitamin D deficiency as 25-hydroxy-vitamin D (25(OH)D) concentrations of <20ng/ml (50 nmol/l) [34].

The current study was conducted to evaluate which factor (Uterine Hypoperfusion or Hypovitaminosis D) has positive correlation to poor pregnancy outcome.

Patient and Methods

Study design and settings: This prospective cohort study was carried out on 300 pregnant women attended the antenatal care clinic and the inpatient wards of Obstetrics and Gynecology Department of Tanta University Hospitals in the period from January 1, 2015 to December 31,2016.

Recruitment: Patients were recruited according to inclusion and

exclusion criteria.

Inclusion criteria were primigravidae, gestational age between 11weeks to 13 weeks, singleton living embryo. Exclusion criteria were patients with normal Vitamin D3 level, patients with missed abortions, any medical diseases (e.g. hypertension, diabetes), or patients with chromosomal aberrations or carrying malformed fetus.

Procedures: Color Doppler velocity measurements were done through the device Siemens sonoline sienna, by using vaginal probe 7 MHz on both right and left uterine arteries at the level of corporio cervical junction and the mean was considered. It is important to ensure that the peak systolic velocity is greater than 60cm/s to ensure the arcuate artery is not being sampled instead of the uterine artery. Pulsatility index (PI) for each waveform was calculated using the software packages on the ultrasound machine. PI is considered abnormal if it is above 95th percentile for gestational [35].

Vitamin D3 was measured in all patients by using a “Dia Sorin Liaison 25OH Vitamin D TOTAL” machine using a chemiluminescence assay to detect total 25-hydroxyvitamin D levels. Levels below 20 ng/mL are considered abnormal.

Patient allocations in cohorts: Patients were first screened by measurement of Vitamin D levels. The cases with normal levels (n=186 cases) were excluded. Patients with hypovitaminosis D (n=114 cases) were examined by uterine artery PI. Patients were then allocated into 2 cohort groups. Group I include patients with hypovitaminosis D (n=79) and abnormal PI while group II included cases with hypovitaminosis D and normal PI (n=55).

Follow up: It was commenced every month with scanning at 20 weeks to 22 weeks for anomaly scan, and continued till 28 weeks then twice weekly till 36 weeks then weekly till delivery. The

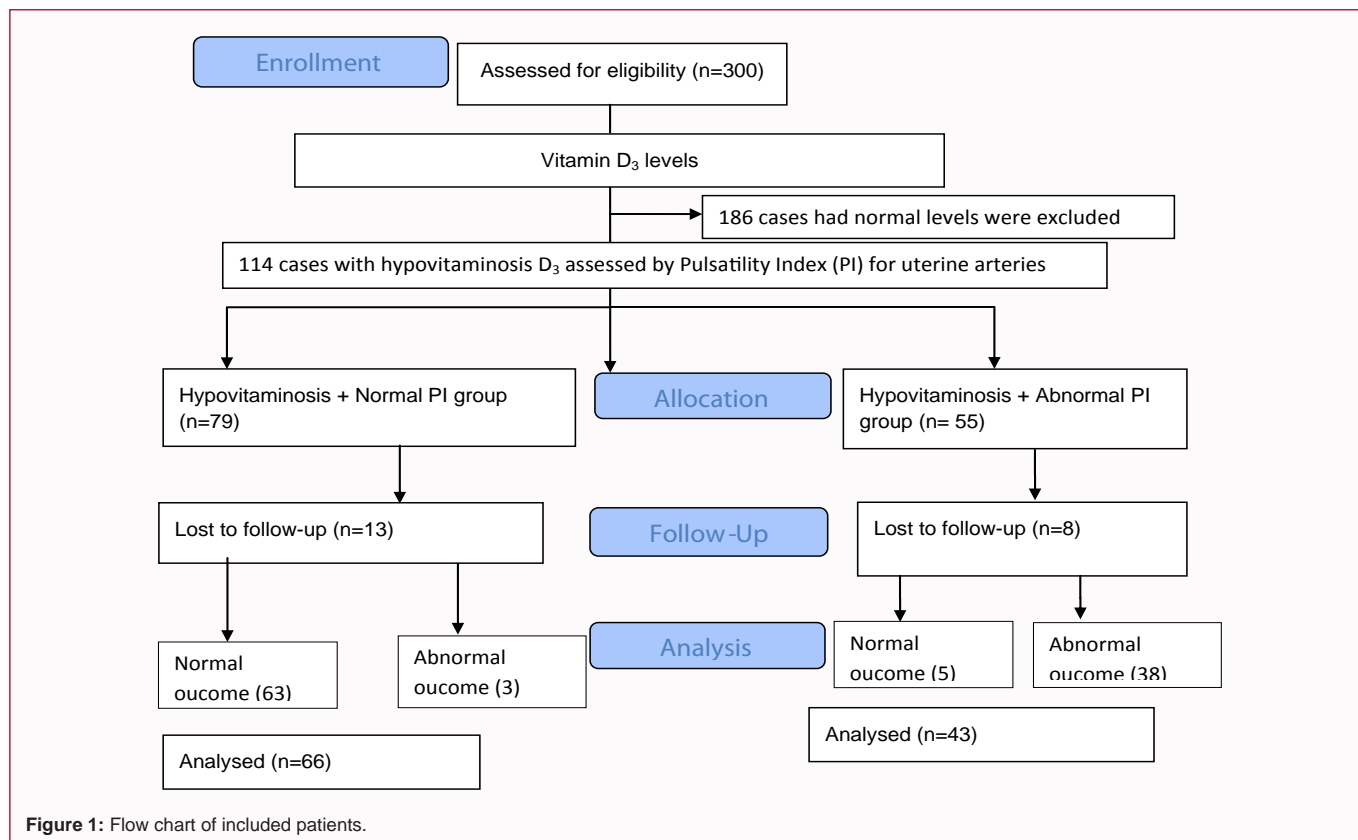


Figure 1: Flow chart of included patients.

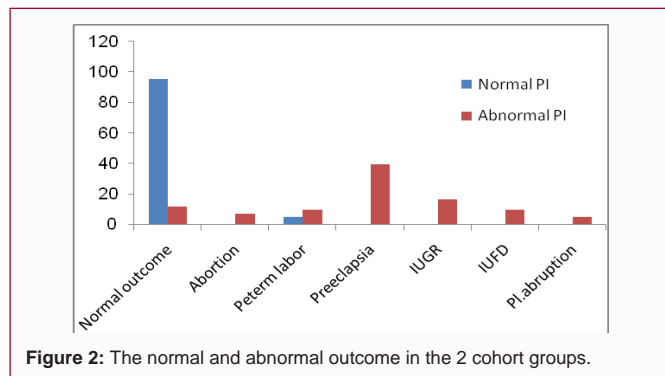


Figure 2: The normal and abnormal outcome in the 2 cohort groups.

Table 2: The correlation of early uterine artery Doppler to outcome of pregnancy CI=95%.

	Normal outcome	Abnormal outcome	P-value
Normal PI (n=66)	63 (95.45%)	3 (4.55%)	0.001*
Abnormal PI (n=43)	5 (11.63%)	38 (88.37%)	0.001*
OR	8.209		<0.001*
RR	19.441		<0.001*
AR	94.85%		

Note: OR: Odd ratio, RR: Relative risk, AR: Attributed risk *: means significant difference.

study outcomes were duration of pregnancy and occurrence of adverse outcomes. These include spontaneous abortion, gestational hypertension, preeclampsia, intra uterine growth restriction, Intra-uterine fetal death, abrupt placenta and spontaneous preterm labor.

Ethical approval: This study was approved by the ethics committee of Tanta University Hospitals before start of study.

Statistical methods: Data were collected and analyzed statistically by mean, SD, chi-square test, unpaired t-test, validity tests (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)). P value <0.05 was considered statistically significant.SPSS Version 20.0 (SPSS Inc., Chicago, IL, USA) statistical package was used to analyze data.

Results

The enrolled patients (n=300) were investigated by Vitamin D3 levels and then normal cases were excluded. The hypovitaminosis D (n=114) were tested by Uterine Pulsatility Index (PI) with resulting 2 cohort groups. The flow chart of patients through the study was shown in Figure 1.

The mean age of enrolled patients were (26.2 ± 4.593) years, the mean BMI was (27.64 ± 3.348) and the mean gestational age at booking was (8.54 ± 1.72) weeks. The demographic data were shown in Table 1.

Follow up of group I (Hypovitaminosis D + Normal PI) revealed that 63/66 (95.45%) ended with normal pregnancy outcome while 3 cases (4.55%) suffered from late preterm labor after 34 weeks with good neonatal outcomes. On the other hand follow up of group II (Hypovitaminosis D + Abnormal PI) revealed that 5/43 (11.63%) ended by normal outcome while the remaining cases 38/43 (88.37%) suffered poor pregnancy outcome as follow: spontaneous abortion (3 cases, 6.98%), preterm labor (4 cases, 9.30%), IUFD (4 cases, 9.30%), preeclampsia (17 cases, 39.53%), IUGR (7 cases, 16.28%), placental abruption (2 cases, 4.65%) Figure 2.

Table 3: Sensitivity, specificity, PPV, NPV of early uterine artery Doppler in prediction of poor pregnancy outcomes.

	Sensitivity	Specificity	PPV	NPV	Accuracy
Abnormal PI	88.37%	95.45%	92.68%	92.65%	92.66%

PPV= Positive Predictive Value, NPV= Negative Predictive Value

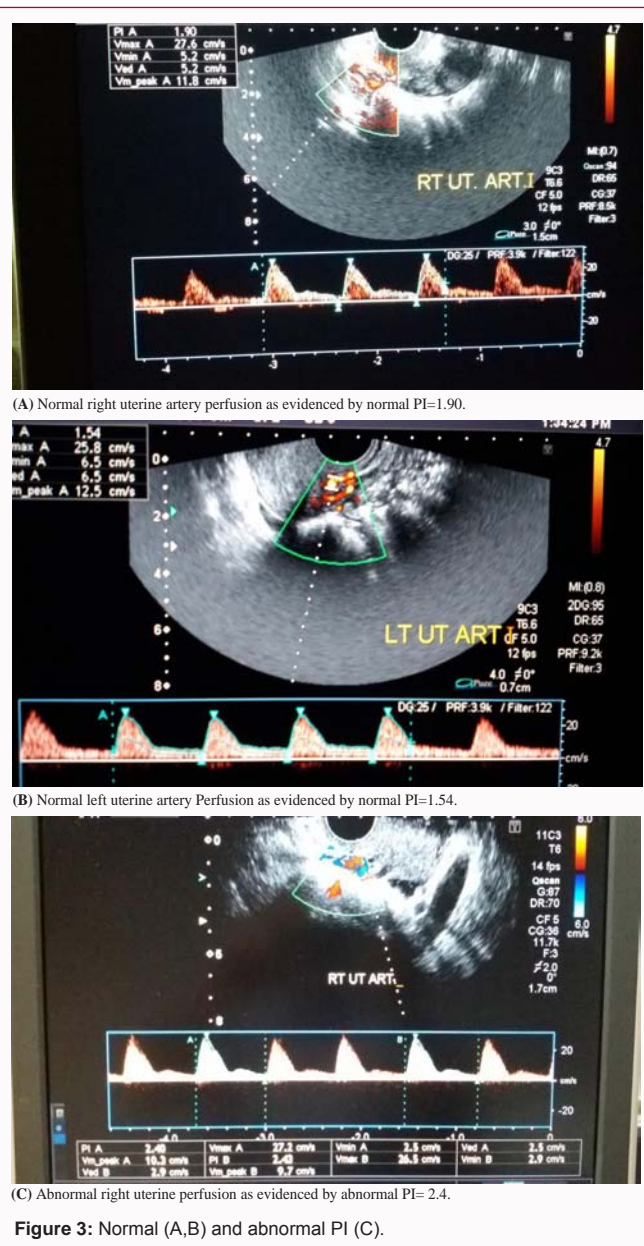


Figure 3: Normal (A,B) and abnormal PI (C).

These results explain the relation of early uterine hypoperfusion for poor pregnancy outcome rather than hypovitaminosis D, OR=12.625, RR=19.422 and AR=94.85% as shown in Table 2.

The sensitivity of abnormal uterine PI (uterine hypoperfusion) was 88.37%, specificity of 95.45%. The PPV was 92.68% and the NPV was 92.65% while accuracy was 92.66% in predicting poor pregnancy outcomes as in Table 3. The normal PI and abnormal PI findings were shown in Figure 3.

Discussion

This study was conducted to evaluate if there is a relation between uterine perfusion, hypovitaminosis D3 and pregnancy outcome. The

enrolled patients were tested by serum vitamin D3 levels and uterine artery Doppler then followed up throughout pregnancy to detect any complications.

It was found that the incidence of vitamin D3 deficiency (< 20 ng/ml) early in pregnancy (11 weeks to 13 weeks) was 38% being present in 114 cases of the enrolled patients. This incidence is higher than that of Nageshu et al. [36] who reported 13.8% of study populations were deficient for vitamin D. Another study was conducted by Karras et al. [28] to assess vitamin D status in Mediterranean region where they found that vitamin D deficiency ranges from 22.7% to 90.3%. They concluded that maternal hypovitaminosis D is prevalent in this sunny area of the world and this was explained by racial, social and cultural habits, as well as the absence of preventive strategies, which negate the benefits of sun exposure [28].

Many studies advocated the use of multiple markers to predict pregnancy outcome in unselected populations. The uterine perfusion assessment and Vitamin D levels were the most commonly tested parameters but with non-conclusive results which were best linked to poor pregnancy outcome [37].

Lisa et al. [38] conducted a study to assess the effect of maternal 25-hydroxyvitamin D [25(OH)D] concentration on the risk of preeclampsia. Patients included were nulliparous pregnant women with singleton pregnancies. They found that adjusted serum 25(OH)D concentrations in early pregnancy were lower in women who subsequently developed preeclampsia.

Evelien et al. [39] explored the association between maternal vitamin D status measured early in pregnancy and birth weight, prevalence of small-for-gestational-age (SGA) infants and postnatal growth (weight and length). Data were derived from a large multi-ethnic cohort in the Netherlands, and included 3730 women with live-born singleton term deliveries. Maternal serum vitamin D was measured during early pregnancy (median 13 weeks, interquartile range: 12-14). Results showed that compared with women with adequate vitamin D levels, women with deficient vitamin D levels had infants with lower birth weights (114.4 g, 95% CI – 151.2, – 77.6) and a higher risk of SGA (OR 2.4, 95% CI 1.9, 3.2).

In this study uterine artery Doppler was done to assess the uterine perfusion, in selected populations of hypovitaminosis D, where normal Doppler findings were found in 79/144 (69.30%) and abnormal Doppler findings were found in 55/114 (30.70%) Figure 1.

Follow up of cases in both groups (Normal and Abnormal Doppler) revealed that poor outcomes were more in hypovitaminosis D and abnormal Doppler where 5/43 (11.63%) ended by normal outcome while the remaining cases 38/43 (88.37%) suffered poor pregnancy outcome as follow: spontaneous abortion (3 cases, 6.98%), preterm labor (4 cases, 9.30%), IUFD (4 cases, 9.30%), preeclampsia (17 cases, 39.53%), IUGR (7 cases, 16.28%), placental abruption (2 cases, 4.65%) Figure 2. On the other hand the group of hypovitaminosis D and normal uterine perfusion was linked to normal outcome in 63/66 (95.45%) and poor outcome in 3/66 (4.55%) Figure 2.

These results were similar to Shakuntala et al. [18] who screened 801 primigravida without past, present obstetric disorder, for uterine perfusion using the resistive Index (RI) where 307 (38.3%) had poor uterine perfusion and 494 (61.7%) were with normal uterine perfusion. They concluded that women with higher uterine artery resistive index in first trimester had more often hypertensive disorders, placental

abruption, oligohydramnios, caesarean births and fetal distress.

In this study, the sensitivity of abnormal uterine PI (uterine hypoperfusion) in predicting poor pregnancy outcome was 88.37%, specificity of 95.45%. The PPV was 92.68% and the NPV was 92.65% while accuracy was 92.66% in predicting poor pregnancy outcomes as in Table 3.

Rampello et al. [19] stated that early evaluation of arterial uterine RI and presence of bilateral notches may be a risk indicator of SGA birth and adverse pregnancy outcome in a high risk population; the specificity is high in the first trimester (0.85 for any adverse outcome); the sensitivity of the test at the first trimester is 0.54 for any adverse outcome (sensitivity in our study was 88.37%); this confirms that uterine artery Doppler examination is linked to poor pregnancy outcome in a selected population of hypovitaminosis D.

The explanations of this study results were that patients with hypovitaminosis D alone had better outcomes as these patients may be exposed to sun later on in pregnancy or may receive multivitamin supplementations later in pregnancy which is common in our country. On the other hand patients with abnormal Doppler had poor outcomes as none of supplementations correct the abnormal uterine perfusion which requires specific supplementation of low dose aspirin.

Limitations of Study

There were some limitations in this study, firstly; some included patients were dropped out and do not complete the follow up schedule. Secondly; there was more than one adverse outcome for a single patient which was analyzed individually to improve the prediction of adverse outcomes.

Conclusion

Hypovitaminosis D alone was not related to poor pregnancy outcomes, while abnormal uterine perfusion early in pregnancy was linked to poor pregnancy outcomes. The sensitivity of abnormal uterine PI (uterine hypoperfusion) in predicting poor pregnancy outcome was high and had higher accuracy.

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