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First Trimester Placental Volume and Uterine Artery Doppler in Pregestational Diabetic and Non-Diabetic Pregnant Women

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Pregestational diabetes is diabetes diagnosed before pregnancy comprises approximately 13 % of all diabetes in pregnancy, while gestational diabetes i.e. diabetes with onset or first recognition in pregnancy comprises the remaining 87%. This work aimed to evaluate the effect of pregestational diabetes mellitus on placental volume and uterine artery Doppler during the late first trimester of pregnancy compared to non-diabetic pregnant women during the same period of gestation.
Methods: This prospective study was conducted on 100 pregnant females from 11 weeks to thirteen 13 weeks gestation. Patients were divided into 2 equal groups: group A included pregnant women with pregestational diabetes mellitus and group B: included non-diabetic pregnant women as a control group. All cases were subjected to clinical examination, laboratory investigations (fasting blood sugar, 2Hrs post-prandial blood sugar, HbA1c and creatinine clearance test) and specific investigations (Mindray DC30 ultrasound and Transabdominal examination).
Results: HbA1c was a positive significant correlation with PI, RI, creatinine clearance and fasting blood sugar, there was a positive significant correlation between fasting blood sugar and PI and RI, there was a positive significant correlation between RI and PI ($P<0.05$).

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Conclusions: Pre-gestational DM does not induce demonstrable alterations in first trimester placental volume, while it induces demonstrable alterations in the first trimester placental development as regards to uterine artery velocimetry Especially PI and RI are significantly increased.

Keywords: First trimester placental volume; uterine artery doppler; pregestational diabetic.

1. INTRODUCTION

Pregestational diabetes is diabetes diagnosed before pregnancy comprises approxi mately 13 % of all diabetes in pregnancy, while gestational diabetes i.e. diabetes with onset or first recognition in pregnancy comprises the remaining 87%. The prevalence of pregestational diabetes has been increasing due to the increasing prevalence of type II diabetes in women of reproductive age, may be due in part to re-classification: some women previously diagnosed with GDM may have been classified as overt diabetes [1].

Maternal diabetes mellitus may affect development and function of the placenta. The placental vessels are in direct continuum with the foetal vascular system and are therefore vulnerable to foetal endocrine derangement [2]. Histological studies have evidenced characteristic changes in the placental vascular structures of diabetic mothers [3].

The maternal and foetal environment influence the complex processes of villous development and placental maturation. In women with pregestational DM, maternal and foetal hyperglycaemia and foetal hyperinsulinemia may act together, or independently, to produce an altered placental vascular phenotype, which includes villous immaturity, villous oedema, presence of basement membrane thickening, congestion of capillaries called “chorangiosis”, intra- and extra-villous fibrinoid and a deposit of glycogen. These observations correspond to mature post-partum placentas [4].

It is well known that the high concentration of circulating glucose and resulting osmotic stress in the embryo that accompany maternal diabetes lead to early retarded embryonic growth and impairs all organ systems [5, 6]. The combination of hyperglycaemia and high oxygen levels reduces proliferation of human first-trimester trophoblasts [6].

The resulting placental anomalies may have deleterious effects for the foetus. There is emerging evidence of epigenetic modulation of foetal endothelial genes in diabetes with long-term vascular consequences [7].

Recent advances in ultrasound by combining 3 D ultrasonography with power Doppler makes it possible to quantify Doppler signals in volumes obtained by 3D scanning and thus allows assessing the whole placental circulation [8].With this technique, it is possible to evidence impaired placental vascularization in different clinical conditions [9].

A relationship between trophoblast proliferation and 3D-PD placental vascularization indices has been demonstrated [10]. In the placenta, these indices potentially reflect both utero placental and fetoplacental blood flow [11].

In the first half of pregnancy, the trophoblast is the key tissue undergoing the most profound changes, while extensive angiogenesis and vascularization occur in the second half of pregnancy, with the endothelium becoming the site of the most important processes [12]. Therefore, the present study was performed in the first trimester of pregnancy. The aim of this work was to evaluate the effect of pregestational diabetes mellitus on placental volume and uterine artery Doppler during the late first trimester of pregnancy compared to non-diabetic pregnant women during the same period of gestation.

2. PATIENTS AND METHODS

This prospective study was conducted on 100 pregnant females from 11 weeks to thirteen 13 weeks gestation, with already established pregestational diabetes mellitus confirmed by history and laboratory investigation (glucose tolerance test) and singleton pregnancy. Multifetal pregnancies, other medical disorders (e.g.: hypertension), drug history of chronic medical disorders, history of severe or lethal fetal malformation and maternal coagulation defect or vascular disease not related to diabetes mellitus were excluded. Patients were divided into 2 equal groups: group A included pregnant women with pregestational diabetes mellitus and group

B: included non-diabetic pregnant women as a control group**.**

Pregnant women were subjected to: Careful history taking, clinical examination, laboratory investigations (fasting blood sugar, 2Hrs post-prandial blood sugar, HbA1c and creatinine clearance test) and specific investigations.

A Mindray DC30 ultrasound machine equipped with a 4-MHz to 8-MHz transabdominal transducer is used for 3D volume scanning during a period of maternal apnea and fetal rest.

Transabdominal examination was carried out Doppler measurement of the uterine artery velocimetry. a sagittal section of the uterus was obtained and the cervical canal and internal cervical os were identified. Subsequently, the transducer was gently tilted from side to side and colour flow mapping was used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insonation is less than 50°. When three similar consecutive waveforms were obtained, the PI and RI were measured and the mean PI and RI of the left and right arteries had been calculated.

Then the entire view of the placenta was identified by two-dimensional ultrasound, and the volume box was adjusted to include the entire placenta. The angle of volume acquisition varies from 45-90° according to placental size. The volume acquisition was obtained in 'maximum' quality and its duration was between 10 and 15 second. For posteriorly and laterally located placentas, a slight lateral inclination of the transducer was performed to acquire the entire placenta. The same pre-established instrument settings were used in all the cases (power 96%; frequency low; quality normal, density 6, ensemble 16; balance 150; filter 2; smooth 3/5; pulse repetition frequency 0.9 kHz, gain_0.2). All placental volumes were acquired, which were aware of diabetic condition of the mother but blind of the metabolic control condition. Successful recordings of placental volume were obtained in all the cases. Placental volumes were stored and later analysed off-line by using the Virtual Organ Computer-aided Analysis (VOCAL) of 3D view software with a 15° rotation step.

2.1 Sample size

Sample Size was calculated using Power and Sample size calculation program at a confidence level of 95% and a power of 80% and based on a previous study carried out by (Moran et al., 2014)(184). which found that placental size in control subjects was 499.6 cm3 while it was 975.0 cm3 in diabetic mothers, and the difference between these two was -475.4 ± 24.46 and accordingly we needed to study 50 patients with Pre-gestational diabetes and 50 control subjects (non-diabetic pregnant women) to be able to reject the null hypothesis.

2.2 Statistical Analysis

Data were fed to the computer using IBM SPSS software package version 21.0. Qualitative data were described using number and percent. Comparison between different groups regarding categorical variables was tested using Chi-square test. Quantitative data were described using mean and standard deviation for normally distributed data. For normally distributed data, comparison between two independent populations were done using independent t-test while more than two populations were analysed F-test (ANOVA) to be used. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

3. RESULTS

There was no significant difference between the two groups regarding maternal, gestational age, BMI and parity. Previous abortion was a significant increase in previous abortion in diabetic group more than the control group (p =0.001). Fasting blood sugar, 2 hr post prandial glucose and HbA1c were significantly higher in group I compared to group II (P=0.001).

There was a significant increase in creatinine clearance, PI and RI in group I more than group II (p =0.001). Placental volume was insignificantly different between two groups.

DM was no significant difference between two groups.

HbA1c was a positive significant correlation with PI, RI, creatinine clearance and fasting blood sugar, there was a positive significant correlation between fasting blood sugar and PI and RI, there was a positive significant correlation between RI and PI.

Table 1. Comparison between the two studied groups regarding the basic demographic, clinical data and the blood glucose profile

		Group I	Group II	T-test	P- Value
Maternal age		30.11± 3.106	31.08±2.481	0.926	0.31
Gestational age (Weeks)		12.04±0.807	11.76± 0.744	1.398	0.082
BMI		28.96±2.541	28.416± 2.560	1.113	0.14
				X^2	P- Value
Parity	1	19(38%)	22(44%)	0.89	0.24
	2	14(28%)	14(28%)		
	3	17(34%)	14(28%)		
Previous abortion	0	33(66%)	45(90%)	4.25	0.001*
	1	15(30%)	5(10%)		
	2	2(4%)	0(0.0%)		
Fasting blood sugar (mg/dl)		149.42±23.024	90.14±8.965	5.01	0.001*
2 hr post prandial glucose (mg/dl)		295.11±42.33	140.22±19.22	4.98	0.001*
HbA1c		6.246±0.345	5.008±0.499	4.11	0.001*

*Data are represented by mean ± SD or number (%), BMI; body mass index, *Significant as p value <0.05, HbA1c: hemoglobin A1c*

Table 2. Comparison between the two studied groups regarding creatinine clearance, placental volume

	Group I	Group II	T-test	P- Value
Creatinine clearance	106.84±18.184	95.1±16.655	3.58	0.001*
Placental volume	50.76±3.51	51.40±3.244	0.98	0.17
PI	0.97±0.146	0.77±0.078	4.09	0.001*
RI	0.69±0.068	0.63±0.070	3.11	0.001*

Data are represented by mean ± SD, PI: Perfusion Index, RI: regular insulin

Table 3. Comparison between the two studied groups regarding Family history of DM

	Group I	Group II	X^2	P value
Family history of DM	12(24%)	7(14%)	1.62	0.202

Data are represented by number (%), DM: Diabetes millets

Table 4: Correlation between different studied variables

		HbA1c	Fasting blood sugar	Creatinine clearance	Placental volume	PI
Fasting blood sugar	Pearson correlation	0.699**				
	P value	0.000				
Creatinine clearance	Pearson correlation	0.329**	0.245*			
	P value	0.001	0.014			
Placental volume	Pearson correlation	-0.110	-0.035	-0.176		
	P value	0.275	0.730	0.080		
	Pearson correlation	0.584**	0.562**	0.067	-0.010	
PI	P value	0.000	0.000	0.507	0.919	
	Pearson correlation	0.297**	0.345**	0.026	0.093	0.224*
RI	P value	0.003	0.000	0.795	0.360	0.025

*PI: Perfusion Index, RI: regular insulin**. Correlation is significant at the 0.01 level. *. Correlation is significant at the 0.05 level*

4. DISCUSSION

Pregestational diabetes is diabetes diagnosed before pregnancy comprises approximately 13 % of all diabetes in pregnancy, while gestational diabetes i.e. diabetes with onset or first recognition in pregnancy comprises the remaining 87%. The prevalence of pregestational diabetes has been increasing due to the increasing prevalence of type II diabetes in women of reproductive age, may be due in part to re-classification: some women previously

diagnosed with GDM may have been classified as overt diabetes [1].

The results of this study showed that there is no statistically significant difference between pregestational diabetic and non-diabetic group as regard maternal age, parity, gestational age, BMI, family history of DM and placental volume.

The results of this study showed that there's statistically significant difference between pregestational diabetic and non-diabetic group as regard number of previous abortion, HbA1c, Fasting blood sugar, 2 hour post prandial glucose, creatinine clearance and vascular indices (PI and RI).

This study showed the correlation between different studied variables, it was found that the level of HbA1c showed a positive significant correlation with PI, RI, creatinine clearance and fasting blood sugar, on the other hand also it was found that there was a positive significant correlation between fasting blood sugar and PI and RI.

In 2011, Higgins et al. [1] conducted a prospective study on (10 women with Type I diabetes), (8 women with Type II Diabetes) and (10 non-diabetic women), aimed to measure the placental volume, length and surface area of placenta. They found that there was no significant statistical difference as regard placental volume (P=0.25) between diabetic and non-diabetic women. This was in agreement with the current study and vascular indices (PI &RI) were increased in diabetic group compared to non-diabetic women, although the small sample size in this study , the increased vascularization may be due to poor glycaemic control (2 women in type II DM with HbAlc >7% and 7 women in type I DM with HbA1C >7%).

In 2011, Odeh et al. [13] conducted a case - control study at the first trimester aimed to measure the placental volume and vascular indices (VI, FI and VFI), patients were classified into two groups (case=120 with pregestational diabetes) and (control=120), they found that there was no significant statistical difference as regard age and the placental volume in agreement to the current study.

Another study in 2012 done by Rizzo et al. [10] in which a prospective observational study was conducted on 32 pregnant women with type I DM at the first trimester of gestation (eleventh 11th and thirteenth 13th week) to evaluate placental volume and vascular indices (VI, FI and VFI), they found that there was no significant statistical difference in the placental volume when compared to reference limits, this is in agreement with the results of the current study but 3D Doppler placental vascular indices were significantly higher in diabetic women (VI P=0.0012:FI P=0,0008 VFI=0.0039) when compared to reference limits.

A prospective case-control study conducted by Gonzalez et al. [14] on pregnant women with pregestational DM and singleton pregnancies at the eleventh 11th week and the thirteenth 13th week of gestation subdivided into 69 women with pregestational DM and the control group comprised 94 pregnant women, showed that no statistical difference was found as regard maternal age , parity and placental volume in agreement with the results of this study but they measured VI, FI and VFI values which were significantly lower in the DM group than in controls (VI p=0.007, FI p=0.003 and VFI p=0.04).

In the study done by Farshchian et al. [15], pregnant women within gestational age of 20 to 40 weeks were consecutively selected. They were in three groups: diabetes mellitus, gestational diabetes, and healthy mothers. They were examined by Doppler ultrasound of the uterine artery and the RI, PI, and PSV were recorded. The data were analyzed using analysis of variance (ANOVA and Kruskal-Wallis tests, resulted in there was no significant difference in terms of the uterine artery RI among the three studied groups (P> 0.05) In contract to the current study. There was a significant difference regarding PI among the three groups (P< 0.05). In agreement with the current study, this may be due to poor glycaemic control, the smaller sample size and measurement of vascular indices in the 2nd & 3rd trimesters.

The results of the current study were in contrast to a 2003 study conducted by Hafner et al. [16] on pregestational diabetic (n 88) aimed to measure placental volume not only at the first but also the second trimester, placental volume (PV) was significantly increased, this may be due to poor glycaemic control (56 patient with HbA1C>7%), the larger sample size and measurement of placental volume in the 2nd trimester.

The results of the current study were in contrast to a study conducted in 2005 by Maly et al. [11] aimed to measure placental volume and vascular indices in pregestational diabetic patients (n 10) compared to controls (n 13) at the first trimester, they found a decrease in placental volume and vascular indices, this may be due to the smaller sample size and poor glycaemic control (5 women had HbA1C>7%) *(12)*.

In 2005, the study performed by Forgas et al. [17] in Doppler studies on 19 women, 10 well-controlled diabetic mothers and 9 normal mothers. All comprehensive obstetrical ultrasound and Doppler evaluations were performed between 28 and 38 weeks' gestation. The following variables were studied: both uterine arteries, umbilical cord and foetal middle cerebral artery. It suggested that the uterine, umbilical cord and foetal middle cerebral artery blood velocity waveforms in uncomplicated and well controlled diabetic pregnancies are similar to control, In contrast to the results of our study, this may be due to the smaller sample size and measurement of vascular indices in the 3rd trimester.

In contrast to the results of this study, De paula et al. [8], conducted a prospective study on pregestational diabetic (n 295) , they found that placental volume increased , this may be due to larger sample size , poor glycaemic control in adition to that values were calculated between 12th and 40 week of gestation (not only at the first trimester).

In contrast to the results of this study another study in 2011 conducted by Odibo et al. [18] on pregestational diabetic (n 49), they found that there was statistically significant difference as regard placental volume, this may be due to higher mean age (over 33 year) in addition to poor glycemic control (HbA1C >7% in 26 patients) *(182)*.

The results of the current study were in contrast to a case - control prospective study conducted in 2016 by Pala et al. aimed to measure placental volume and placental mean gray value in gestational diabetes mellitus (GDM) and healthy control patients using three-dimensional (3D) ultrasound and Virtual Organ Computer-aided.

5. CONCLUSIONS

Pre-gestational DM does not induce demonstrable alterations in first trimester placental volume, while it induces demonstrable alterations in the first trimester placental development as regards to uterine artery velocimetry Especially PI and RI are significantly increased.

CONSENT

All patients signed an informed consent.

ETHICAL APPROVAL

This study was approved by the ethics committee of Tanta University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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