The Egyptian Journal of Hospital Medicine (October 2017) Vol.69 (3), Page 2043-2051

First Trimester Placental Volume and Vascular Indices by 3D Ultrasonography and 3D Power Doppler in Pregestational Diabetic and Non-Diabetic Pregnant Patients

Magd E. Mohamed, Amr M. Elhelaly, Mahmoud H. Abdelfattah
Department of Obstetrics and Gynecology,Faculty of Medicine - Ain Shams University

ABSTRACT

Background: 3D power Doppler ultrasonography enables the quantitative analysis of the region observed through vascular indices as VI (vascularization index), FI (flow index) and VFI (vascularization flow index), which show the quantity of vessels, the local blood flow and their combination and placental volume. These indices can be calculated using VOCAL program. **Aim of the Study:** This study aimed at comparing placental volume and vascular indices using 3D ultrasonography and 3D power Doppler in pregestational diabetic and non-diabetic pregnant women at the first trimester (11^{th} week and 13^{th} week). **Patients and Methods:** This current study was conducted at Antenatal care Clinic in cooperation with "the feto-maternal Unit for ultrasound assessment", Ain-Shams University Maternity Hospital during the period between **November 2015** and **April 2017**, on 46 women at the **eleventh 11^{th} week** and **thirteen 13^{th} week** of gestation. They were divided into two groups: Group (A) included 23 women with pregestational diabetes mellitus and group (B) included 23 non-diabetic pregnant women as a control group after respecting certain inclusion and exclusion criteria. **Results:** There was no statistically significant difference between pregestational diabetic and non - diabetic group as regard placental volume and vascular indices (VI, FI and VFI). **Conclusion:** There was no statistically significant difference as regard placental volume and vascular indices (FI,VI and VFI) in pregestational diabetic compared to non-diabetic pregnant patients at the first trimester of pregnancy especially with good glycemic control but changes may be present with poor glycaemic control. **Recommendations:** Further studies are recommend as regard evaluating placental volume and vascular indices (FI,VI and VFI) in pregestational diabetic at the second and the third trimester of pregnancy giving more time for the pathological effect of diabetes mellitus to appear.

Keywords: first trimester placental volume, vascular indices, 3D ultrasonography, 3D power Doppler.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia and caused by defects in insulin secretion and /or insulin action [(1)]. Diabetes mellitus is a major public health problem worldwide. Its prevalence has been used as one of the parameters in the assessment of the quality of health care by the world health organizations (WHO)[(2)] .In 1842, an Austrian professor of mathematics and geometry Dr. Christian John Doppler first described in detail the effect that now bears the name. Satomura was the first describing clinical application of Doppler ultrasound technology in 1959 [(3)].The placenta is an essential link between the mother and the developing fetus, and histological studies have evidenced characteristic changes in the placental vascular structures of diabetic mothers**[(4)].** The umbilical artery was the first vessel studied by obstetric Doppler examination. Flow velocity waveforms from the umbilical artery represent the downstream or placental resistance to flow. Umbilical artery resistance decreases progressively throughout gestation, reflecting the increase and dilation in villous vascularization**[(5)].** Doppler US offers a unique non - invasive technology for investigating the circulatory system. Doppler ultrasound velocimetry has been extensively used to investigate fetal, feto-placental and utero placental circulation. There is ample evidence associating abnormal Doppler findings with complication of pregnancy and an adverse perinatal outcome [(6)].The advent of three-dimensional (3D) power Doppler ultrasound has begun a new era in tissue and organ vascularization research Therefore, we can calculate vascular indices using the specially Designed VOCAL TM software**[(7)].** Doppler examinations of intra placental blood circulation appear to be an efficient method for diagnosing and managing pregnancies complicated by fetal intrauterine growth restriction (IUGR), because the changes in maternal Doppler findings (i.e., uterine artery) and in fetal Doppler (i.e., umbilical artery) are secondary to the changes in the placental vascular tree**[(8)].**

Objective and non-invasive quantification of vascularization of a given tissue volume holds much promise, particularly because this method has proved to be highly reproducible between observers (thereby overcoming one of the main limitations of conventional Doppler ultrasound)**[(9)].**

Received: 14 / 7/2017
Accepted: 23 / 7 /2017
DOI : 10.12816/0041057

Recent advances in ultrasonography was by combining 3Dultrasonographywithpower Doppler makes it possible to quantify Doppler signals in volumes obtained by 3D scanning and thus allows to assess the whole placental circulation, with this technique, it is possible to impaire placental vascularization in different clinical conditions[(10)].

Rizzo et al. [(11)] investigated the placental volume and vascular indices using 3D ultrasonography&3D power Doppler in pregestational diabetic mothers during the first trimester and concluded that placental vascular indices (VI ,FI and VFI) are increased and are more evident in pregnancies with poor first trimester glycemic control.3D ultrasound was patented by ***von Ramm and Stephen Smith***[(12)] at Duke University in 1987**.** 3D ultrasound has the potential to provide improved visualization of the fetal anatomic morphology compared to the conventional 2D imaging.3D ultrasound and power Doppler give a more objective and more detailed method of evaluating placental volume and its vascular network. The first placental volumes acquired via sonography were conducted by***Brinkley et al.***[(13)]**.**

The Doppler parameters derived from 3D interrogation of the placenta are different, include the Vascularization index (VI) that characterizes vessels' density, the flow index (FI) that characterizes blood flow intensity and the vascularization flow index (VFI) that evaluate simultaneously the vessels and perfusion[(14)]**.**

The 3D power Doppler allows the assessment of the architecture of the placental tree [(15)]**.** Utero placental and feto placental perfusion have been extensively studied throughout gestation and after delivery. Direct investigation of the perfusion of in-vivo placentae has become possible using three-dimensional (3D) power Doppler sonography [(16)].

3D power Doppler does not take long to consider the possibility of a quantitative vascular analysis of the region observed. This was analyzed through the vascular indices as VI (vascularization index), FI (flow index) and VFI (vascularization flow index), which show the quantity of vessels, the local blood flow and their combination [(17)].

The pre-determined area was formed of small pieces of volume named voxels. From then on, they were divided into gray voxels, pieces that compose the non colored part of the three-dimensional area with black and white tones, and colored voxels, formed by the colored part of this section, both measured in a scale of 0–100 [(18)]**.** Nowadays, all these indices can be calculated in a pre-determined area, through a program that is followed in a series of three-dimensional ultrasound machines named VOCAL (virtual organ computer-aided analysis) [(16)].

The vascularization of the placenta was evaluated through these indices at specific locations, because the research of the placenta, at advanced gestational ages (first trimester excluded), is impossible due to their dimensions [(19)]. Three-dimensional (3D) ultrasonography allows examiners to move from a 3D mental reconstruction of two-dimensional (2D) images to actual 3D visualization of anatomical structures [(20)]. Thus, sonologists are no longer constrained by limitations of static 2D images to establish a diagnosis, but can, instead, interact with volume data sets to examine anatomical structures of interest in planes of section other than the original acquisition planes [(21)].

Color and power Doppler techniques permit direct visualization of placental vascularity, allowing assessment of both the utero placental and feto placental circulations. Poor vascularity secondary to uterine scarring or large fibroids can lead to atrophy of the chorionic villi and corresponding compromise of fetal circulation [(22)]**.**

AIM OF THE WORK

To compare placental volume and vascular indices (VI, FI and VFI) using 3D Ultrasonography and 3D Power Doppler in pregestational diabetic and non-diabetic pregnant patients at the first trimester (**the eleventh 11th week** and **the thirteenth 13th week**).

Patients and Methods

This case - control study was carried out at the Antenatal care Clinic in cooperation with "the feto-maternal Unit for ultrasound assessment", Ain-Shams University Maternity Hospital during the period between **November 2015** and **April 2017**, on 46 women at the **eleventh (11th)week** and **thirteenth (13th)week** of gestation, divided into two groups:

group (A) included 23 women with pregestational diabetes mellitus and group (B) included 23 non-diabetic pregnant women as a control group.

The study protocol and patient informed consent were declared for ethical and research approval by the Council of Obstetrics and Gynaecology Department, Ain Shams University.

Sample size justification

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 ***Khaskhelli et al.,*** [(23)] 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±23.46 and accordingly we needed to study 23 patients with Pre-gestational diabetes and 23 control subjects (non-diabetic pregnant women) to be able to reject the null hypothesis.

Inclusion criteria

- Singleton pregnancies.
- Confirmed pregestational diabetes mellitus by history and laboratory investigation (FBS - 2h PPBS - HbA1C).
- Absence of fetal structural or chromosomal anomalies.

Exclusion criteria

- Multifetal pregnancies.
- Women with other medical conditions eg. (chronic heart disease, chronic hypertension, chronic renal insufficiency and any other chronic illnesses) were excluded from the study.

All pregnant women included in the study underwent the following:

History taking

At the initial visit, a detailed history was obtained including personal history and past history concerning:

- 1st day of Reliable last Menstrual Period to calculate gestational age according to Naegle`s rule.
- Family history of DM.
- Any history suggestive of pregestational diabetes as abortion,repeated, unexplained IUFD or fetal macrosomia.
- History of chronic heart diseases, chronic hypertension, thyroid disease, chronic renal in sufficiency, hepatic disease, thrombophilia and systemic lupus erythematosus.

Clinical examination

Careful general clinical examination including body weight, blood pressure, lower limb edema, maternal body mass index and abdominal examination.

Laboratory investigations

Including FBS, 2hPPBS, HbA1C,CBC, liver (ALT-AST and albumin) and renal (s.urea and creatinine)function tests and urine analysis.

Specific investigations

At the first trimester of gestation **(11th week and 13th week)**, we calculated placental volume by 3D ultrasonography and calculated vascularization index, flow index and vascularization flow index by 3D power Doppler, the machine used in the study was **VolusonE6BT12**(general electric) with convex probe-RAB -6 D curved array.

A Voluson E6BT12 ultrasound machine equipped with a 4-MHz to 8-MHz trans-abdominal transducer was used for 3D volume scanning during a period of maternal apnea and fetal rest. 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 varied 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 analyzed off-line by using the Virtual Organ Computer-aided Analysis (VOCAL) of 3D view software with a 15_ rotation step. Vascularization index (VI), flow index (FI), and velocity flow index (VFI) were calculated.

Statistical analysis

- Qualitative data was presented as numbers and percentages while quantitative data was presented as Mean and standard deviation.
- Comparison between the means of two independent groups was performed using independent sample t-test.
- Comparison between numbers and percentages was performed using chi-square test, if 25% of the cells or more expected frequency less than 5 Fisher Exact test was used.
- Differences were considered to be statistically significant if p-value <0.05.
- Statistical analysis was undertaken using SPSS(statistical program for social science).

RESULTS

The current study was conducted on 46 women (23 pregestational diabetic and 23 non-diabetic)attending the antenatal care clinic in cooperation with the"feto-maternal unit for ultrasound assessment" Ain-Shams University Maternity hospital during the period between November (2015) and April (2017) to calculate placental volume and vascular indices at the first trimester of gestation (the 11thweekand 13th week)

by 3D power Doppler ultrasonography after respecting certain inclusion and exclusion criteria.

Table (1): Comparison between Diabetic and Non-Diabetic women as regard VI at the eleventh 11th week.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
VI	**Non-diabetic**	12.1359	2.62390	-1.494	0.142
	Diabetic	17.6987	2.62361		

VI= Vascularization index
p>0.05 ➔ Non-Significant
p<0.05 ➔ Significant
p<0.001 ➔ Highly Significant

Table (1) shows that the mean VI at **theeleventh11th week** in Diabetic group (12.1359 ± 12.62390) was higher than non-diabetic group(17.6987 ± 12.62361); however there is a statistically insignificant difference between diabetic and non-diabetic women as regard VI at **the eleventh 11th week** (P>0.05).

Table (2): Comparison between Diabetic and Non-Diabetic women as regard FI at the eleventh 11th week.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
FI	**Non-diabetic**	34.5942	9.65622	-2.004	0.051
	Diabetic	40.7201	11.03053		

FI= Flow index
p>0.05 ➔ Non-Significant
p<0.05 ➔ Significant
p<0.001 ➔ Highly Significant

Table (2) shows that the mean FI at **the eleventh 11th week** in Diabetic group(40.7201 ± 11.03053) was higher than non-diabetic group(34.5942± 9.65622); however there is a statistically near significant difference between diabetic and non-diabetic women as regard FI at **the eleventh 11th week** (P>0.051),may be large sample size show significant difference.

Table (3): Comparison between Diabetic and Non-Diabetic women as regard VFI at the eleventh 11th week

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
VFI	**Non-diabetic**	6.5221	1.19599	-0.384	0.703
	Diabetic	7.7670	2.36749		

VFI= Vascularization Flow index
p>0.05 ➔ Non-Significant, p<0.05 ➔ Significant, p<0.001 ➔ Highly Significant

Table (3) shows that the mean VFI at **the eleventh 11th week** in Diabetic group(7.7670± 6.36749) was higher than non-diabetic group(6.5221± 14.19599); however there is a statistically insignificant difference between diabetic and non-diabetic women as regard VFI at **the eleventh 11th week** (P>0.05).

Table (4): Comparison between Diabetic and Non-Diabetic women as regard Placental volume at the eleventh 11th week.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
Placental volume/cm3	**Non-diabetic**	27.5304	7.45907	0.132	0.895
	Diabetic	26.9004	4.74398		

p>0.05 ➔ Non-Significant
p<0.05 ➔ Significant
p<0.001 ➔ Highly Significant

Table (4) show that the mean Placental volume at **the eleventh 11th week** in Diabetic group(26.9004± 14.74398) was lower than non-diabetic group(27.5304± 17.45907); however there is a

statistically insignificant difference between diabetic and non-diabetic women as regard Placental volume at **the eleventh 11th week**(P>0.05)

Table (5): Comparison between Diabetic and Non-Diabetic women as regard VI at the thirteenth 13thweek.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
VI	**Non-diabetic**	16.3664	4.17095	-0.040	0.968
	Diabetic	16.5110	3.81227		

VI=Vascularization index
p>0.05 ➔ Non-Significant, p<0.05 ➔ Significant, p<0.001 ➔ Highly Significant

Table (5) shows that the mean VI at the **thirteenth 13th week** in Diabetic group (16.5110 ± 9.81227) was slightly higher than non-diabetic group(16.3664 ± 14.17095); however there is a statistically insignificant difference between diabetic and non-diabetic women as regard VI at the **thirteenth 13thweek** (P>0.05).

Table (6): Comparison between Diabetic and Non-Diabetic women as regard FI at the thirteenth 13thweek.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
FI	**Non-diabetic**	40.2874	7.52382	-0.562	0.579
	Diabetic	42.5189	7.47494		

FI=Flow index
p>0.05 ➔ Non-Significant, p<0.05 ➔ Significant, p<0.001 ➔ Highly Significant

Table (6) shows that the mean FI at the **thirteenth 13th week** in Diabetic group(42.5189 ± 7.47494) was higher than non-diabetic group(40.2874 ± 17.52382); however there is a statistically insignificant difference between diabetic and non-diabetic women as regard FI at the **thirteenth13thweek** (P>0.05).

Table (7): Comparison between Diabetic and Non-Diabetic women as regard VFI at the thirteenth 13thweek.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
VFI	**Non-diabetic**	8.1196	2.54738	0.571	0.572
	Diabetic	7.0832	2.35210		

VFI= Vascularization Flow index
p>0.05 ➔ Non-Significant, p<0.05 ➔ Significant, p<0.001 ➔ Highly Significant

Table (7) shows that the mean VFI at the **thirteenth 13th week** in Diabetic group(7.0832 ± 4.35210) was lower than non-diabetic group (8.1196± 7.54738); however there is a statistically insignificant difference between diabetic and non-diabetic women as regard VFI at the **thirteenth 13thweek** (P>0.05).

Table (8): Comparison between Diabetic and Non-Diabetic women as regard Placental volume at the thirteenth 13thweek.

U/S Indices	Group	Mean	Standard Deviation	Independent sample t-test	P-value
Placental volume/cm3	**Non-diabetic**	54.4592	7.84787	0.457	0.650
	Diabetic	52.0443	7.95270		

p>0.05 ➔ Non-Significant, p<0.05 ➔ Significant, p<0.001 ➔ Highly Significant

Table (8) shows that the mean Placental volume at the thirteenth 13th week in Diabetic group(52.0443 ± 17.95270) was lower than non-diabetic group(54.4592 ± 17.84787); however there is a statistically insignificant difference between diabetic and non-diabetic women as regard Placental volume at the thirteenth 13thweek (P>0.05).

DISCUSION

The current study was conducted at the antenatal care clinic in cooperation with "the feto-maternal Unit for ultrasound assessment", Ain-Shams University Maternity Hospital during the period between **November (2015**) and **April**

(2017), included 46 pregnant women subdivided into two groups
Group (A) 23 Pregestational Diabetic women
Group (B) 23 Non – Diabetic pregnant women

To compare placental volume and vascular indices (VI, FI and VFI) between the two group at the first trimester of gestation (the eleventh 11thweek and the thirteenth 13thweek) Using 3D ultrasonography and 3D power doppler.

The results of this study showed that there is no statistically significant difference between pregestational diabetic and non-diabetic group as regard age, parity number. of abortions, gestational age, placental volume and vascular indices (VI and VFI only) except FI which showed near statistical significance value(P>0.051), may be larger sample size would show significant difference.

A prospective case-control study conducted by ***Gonzalez et al.*** **(24)** on pregnant women with pregestational DM and singleton pregnancies at the eleventh 11th week and the thirteenth 13thweek of gestation subdivided into 69 women with pregestational DM (44 with type I DM and 25 with type II DM) and the control group comprised 94 pregnant women, showed that no statistical as regard age ,parity and placental volume except for vascular indices, (VI,FI and VFI) were significantly reduced among the diabetic group **in contrast to** the results of this study. The difference may be attributed to the larger sample size in this study (163 women) and the diabetes mellitus control of the patients, As regard HbA1Cof the other study (60 women had HbA1C more than 7%), but all patients in the current study had HbA1C less than 7% (well-controlled). ***Monlár et al.,*** **(25)** conducted a study between 2011 and 2013 to evaluate the vascular indices (VI, FI and VFI)at the first trimester of pregnancy. The pregnancies were divided into two groups: I. non-pathological control group (n=113) and II. case group comprising pregnancies complicated by two subgroups of diabetes mellitus (n=99): II.a) Type I DM (n=43) and II.b) GDM (n=56).

They found no significant statistical difference as regard maternal age and gestational age, but showed that all three placental vascular indices (VI, FI and VFI) were significantly reduced among diabetic pregnant women as compared to the control group (p<0.001)**.In the above mentioned results**, this difference may be attributed to the larger sample size(n 212) and the poor glycaemic control (32 patient of type I DM and 15 patient of GDM had HbA1Cmore than 7%). ***Rizzo et al.,*** **(11)** conducted a prospective observational study on 32 pregnant women with type I DM at the first trimester of gestation (eleventh 11thand thirteenth 13thweek) 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 (VIP=0.0012:FIP=0,0008VFI=0.0039) when compared to reference limits **in contrast to** the current study p-value>0.05,this difference may be attributed to the larger sample size and the glycaemic state of the patients included in the study (9 patients had HbA1Cmore than 7%).

Raine-Fenning et al., **(26)** conducted a study on pregestational diabetic patients (n 220)at the first trimester (11weeks and 14 weeks).**In contrast to the results of this study,** they found that vascular indices (VI, VFI) increased while FI reached a peak with three vessels (uterine, middle cerebral. umbilical) and then decreased, this may be due to the larger sample, machine settings used (voluson 730), the poor glycaemic state of patients (45 women had HbA1Cmore than 7%), moreoverthey measured vascular indices on three vessels (we used umbilical vessels only).

The results of this study were **in agreement with** a study conducted in ***Taipei Veterans General Hospital*** (Taiwan) on a total of 222 women with singleton pregnancy from the eleventh 11thweek to the thirteenth 13thweek. All the indices, including the mean gray value (MGV) showed no significant statistical difference. Although this study was conducted on a larger sample size, and measured the mean gray value (placental density)but the glycemic state of most of the patients were well – controlled (only 4 women had HbA1C more than 7%).

The results of the current study were **in contrast to** a case - control prospective study conducted by ***Pala et al.*** **(27)** 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 Analysis (VOCAL) in 39 singleton pregnancies complicated by GDM and 42 healthy singleton pregnancies matched for gestational age, maternal age and parity. Placental volume was significantly larger in GDM (411.59 ± 170.82 versus 343.86 ± 128.94 cm3; p value = 0.046).this may be due to larger sample size and also the patient in the current study were well-known and controlled pregestational diabetic (not gestational diabetes mellitus). **In agreement with the results of this study** ***Salvesen et al.*** **(28)** conducted a cross-

sectional study on 65 well - controlled diabetic pregnancies. ,They found that the placental vascular indices (VI, FI and VFI) measured by 3D power doppler ultrasonography showed no statistical significant difference except when complicated with preeclampsia or fetal growth restriction(FGR).

In contrast to the results of the current study, *Jauniaux and Burton*[29] conducted a study on pregestational diabetic (n 66) at the first trimester, they found an increase in vascular indices (VI, FI and VFI), this may be due to poor glycaemic control (HbA1C >7% in 37 patients), in addition to the larger sample size.

In contrast to the results of this study another investigation was conducted by ***Hafner et al.*[30]** on pregestational diabetic (n 356), they found an increase in placental volume, this may be due to larger sample sizeand values wereobtainedat the first and the second trimester.

In contrast to the results of this study *De paula et al.*, [31], conducted a prospective study onpregestational diabetic (n 295), they found that placental volumeand vascular indices (VI, FI and VFI)increased, this may be due to larger sample size, poor glycaemic control in adition to thatvalueswere calculatedbetween 12th and 40 week of gestation (not only at the first trimester).

In contrast to the results of this study another study conducted by ***Odibo et al.*[32]** on pregestational diabetic (n 49),they found that there was statistically significant difference as regard placental volume and vascular indices (VI, FI and VFI), this may be due to higher mean age (over 33 year) in addition to poor glycaemic control (HbA1C >7% in 26 patients).

***Martins et al.*,[33],**conducted a study on pregestational diabetic patients(n 65) at the first trimester (11thand 13thweek) aimed to measure vascular indices (VI, FI and VFI) with 3D power Doppler ultrasonography which were significantly reduced **in contrast to the results of the current study**, this may be due to high body mass index (BMI) more than 30kg/m2but our patients were with average BMI because (the values of vascular indices are affected by the depth between area of analysis and the probe).

***Odeh et al.*, [34]**,conducted a case - control study at the first trimester aimed at measuring 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, gestational age, (PV), (FI) and (VFI) **in agreement to the current study** except for (VI)which was significantly reduced, this may be due to poor glyacemic control (HbA1C >7%in 45 patient), in addition to the larger sample size.

***Higgins et al.*,[35],**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 **but** vascular indices (VI,FI and VFI) were **increased** in diabetic group compared to non-diabetic women (P=0.002), 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 HbAIC >7% and 7 women in type I DM with HbA1C >7%).

The results of the current study were **in agreement with** a study conducted by ***De Paula et al.*[10]** (no significant statistical difference in VI, FI and VFI), where the entire placenta was identified as in the current study but were **in contrast to** a study conducted by ***Merce´ et al.*[36]** which found an increase in VI, FI and VFI, this may be due to that they identified only a part of the placenta with the highest density of vessels, a technique called ‘‘vascular placental biopsy’’, and also were **in contrast to** a study conducted by ***Guiot et al.*[37]** which found a decrease inVI, FI, and VFI, this may be due to the calculated vascular indices (VI,FI and VFI) in five constant region of the placenta.

The results of this study were **in contrast to** those of ***Yu et al.*[38]** Which revealed a decrease in vascular indices(VI, FI and VFI) measured at the first trimester on pregestational diabetic (n77type I DM=43 and type II DM=30),this may be due to **higher mean age of patients** (over 30 year) and **vascular indices (VI,FI and VFI) were calculated for a fixed placental volume**, in addition to the larger sample size.

The results of the current study were **in contrast to** those of a study conducted by ***Maly et al.*[39],** aimed to measure placental volume and vascular indices (VI,FI and VFI) in pregestational diabetic patients (n 10) compared to controls (n 13) at the first trimester, they found a decreasein placental volume and vascular indices, this may be due to the smaller sample sizeand poor glycaemic control (5 women had HbA1C>7%).

The results of the current study were **in contrast to** Those observed by by ***Lai et al.* [40], *and Negrini et al.* [41]** on pregestional diabetic (n 100), who found significant statistical difference as regard vascular indices (VI, FI and VFI),, this difference may be attributed to the glycaemic state

(37 patient had HbA1C >7%), difference in the machine settings used (voluson730 expert), higher mean ageof patients (over 32 year) and higher mean of parity (over 4).

The results of the current study were **in contrast to** The data of ***Hafner et al.*** [30] on pregestional diabetic (n 88) Who measured 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. **Finally**, from most of the above studies we found that the distinct placental changes associated with diabetes mellitus depend on the gestational period.In early pregnancy . The high glucose level triggers vasculogenesis but vasculopathy is not present yet. In later stage of pregnancy the vasculopathy affects the blood flow in the placenta, especially in poor glycaemic control. **Therefore, it is worth to display the usefulness of measuring vascular indices (VI, FI and VFI) and placental volume in pregestational diabetic at the first trimester was limited especially with good glycaemic control**, also Differences in methodology of placental volume acquisition, machine settings, and sample sizes of the studies may contribute to the different results. In addition, the machine settings may influence the quantitative values obtained from 3D power Doppler interrogation of the placenta.

CONCLUSION

There was no statistically significant difference as regard placental volume and vascular indices (FI,VI and VFI) in pregestational diabetic compared to non-diabetic pregnant patientsat the first trimester of pregnancy especially with good glycemic control but changes may be present with poor glycaemic control.

RECOMMENDATIONS

We recommend to conduct further studies as regard evaluating placental volume and vascular indices (FI,VI and VFI) in pregestational diabetic at the second and the third trimester of pregnancy giving more time for the pathological effect of diabetes mellitus to appear.

Flow index (FI) among vascular indices (VI and VFI) was near significant, so we also recommend a larger sample size in future studies.

REFERENCES

1) **Metelko Z, Renar P, Poljicanin T *et al.* (2008):** Prevalence of diabetes mellitus in Croatia. Diabetes research and clinical practice, 81(2):263-7.

2) **American Diabetes Association (2007):** Nutritional standards for diabetes self-management education. Diabetes Care, 30 (1):S96-S103.

3) **Rosenberg JC (1997):** Doppler ultrasound of the normal fetus. In: Diagnostic medical sonography. A guide to clinical practice of obstetrics and gynecology. Berman M and Cohen HL. Lippincott, Philadelphia, New York, second edition, Pp 399-415.

4) **Nelson SM, Coan PM, Burton GJ et al. (2009):** Placental structure in type 1 diabetes: relation to fetal insulin, leptin and IGFI. Diabetes, 58: 2634–41.

5) **Tan TY, Taylor MJ, Wee LY, Vanderheyden T, Wimalasundera R, Fisk NM (2009*):*** Doppler for artery – artery anastomosis and stage-independent survival in twin – twin transfusion. Obstet Gynecol., 103:1174–1180.

6) **Nicolaides K, Rizzo G, Hechker K *et al.* (2002*):*** Doppler in Obstetrics. Fetal Medicine; ISUOG Educational Series, Available at: https://fetalmedicine.org/var/uploads/Doppler-in-Obstetrics.pdf

7) **Raine-Fenning NJ, Clewes JS, Kendall NR *et al.* (2003*):*** The inter-observer reliability and validity of volume calculation from three-dimensional ultrasound data sets in the in vitro setting. In: Ultrasound Obstet Gynecol., 21:283-91.

8) **Abramowicz JS, Sheiner E (2008):** Ultrasound of the placenta: a systematic approach. Part I: imaging. Placenta, 29:225–240.

9) **Jarvela IY, Sladkevicius P, Tekay AH, Campbell S, Nargund G (2003):** Intraobserver and interobserver variability of ovarian volume, gray-scale and color flow indices obtained using transvaginal three-dimensional power Doppler ultrasonography.Br Med J., 21:277-282.

10) **De Paula CF, Ruano R, Campos JA, Zugaib M (2009):** Quantitative analysis of placental vasculature by three-dimensional power Doppler ultrasonography in normal pregnancies from 12 to 40 weeks of gestation. Placenta, 30:142-8.

11) **Rizzo G, Capponi A, Pietrolucci ME *et al.* (2012*):*** First trimester placental volume and three dimensional power Doppler ultrasonography in type I diabetic pregnancies. Prenatal Diagnosis, 32: 480–484.

12) **Von Ramm, Olaf T, Smith, Stephen W (1987):** "Three-dimensional imaging system". United States patent US 4,694,434. Available at : https://www.google.com/patents/US4694434

13) **Brinkley JF, McCallum WD, Muramatsu SK *et al.* (1984*):*** Fetal weight estimation from lengths and volumes found by three-dimensional ultrasonic measurements. Ultrasound Med**.,** 3(4):163-8.

14) **Matijevic R, Kurjak A (2002):** The assessment of placental blood vessels by three-dimensional power Doppler ultrasound. J Perinat Med., 30:26–32

15) **Hata T, Kanenishi K, Akiyama M *et al.* (2005):** Real-time 3-D sonographic observation of fetal facial expression. In: J Obstet Gynaecol Res., 31:337-40.

16) **Kurjak A, Hafner T, Kupesic S, Kostovic L (2002):** Three-dimensional power Doppler in study of embryonic vasculogenesis.J Perinat Med., 30: 18–25

17) Pairleitner H, Pretorius DH, Borok NN, Coffler MS, Nelson TR (2010): Three-dimensional ultrasound in obstetrics and gynecology. Radiol Clin North Am., 39: 499–521.

18) Staudach A, Kurjak A, Funduk-Kurjak B, Bekavac I (2008): Assessment of early chorionic circulation by three-dimensional power Doppler.J Perinat Med**.,** 30: 33–39.

19) **Zalud I and Shaha S (2007):** Evaluation of utero-placental circulation by three-dimensional Doppler ultrasound in the second trimester of normal pregnancy. J Matern Fetal Neonatal Med., 20(4): 299-305.

20) Benacerraf BR, Shipp TD, Bromley B (2009): How sonographic tomography will change the face of obstetric sonography: a pilot study. J Ultrasound Med., 24: 371–378.

21) Merz E, Bahlmann F, Weber G, Macchiella D (2005) : Three-dimensional ultrasonography in prenatal diagnosis. JPerinat Med., 23:213–222.

22) Lax A, Prince MR, Mennitt KW, Schwebach JR and Budorick NE (2007): The value of specific MRI features in the evaluation of suspected placental invasion. Magn Reson Imaging, 25(1):87–93.

23) Khaskhelli L, Memon S, Goswami P, Bano S (2013): Change in Normal Morphology of Placenta and Its Possible Effects on Fetal Outcome in Diabetic Mothers as Compared to Non-Diabetic Mothers, JLUMHS., 12(01):49.

24) Gonzalez G, Davila G, Csatro A *et al.* (2014): Effect of pregestational diabetes mellitus on first trimester placental characteristics: Three-dimensional placental volume and power Doppler indices. Placenta, 35(3): 147-51.

25) Molnár A, Surányi A, Nyári T, Németh G, Pál A (2014): Examinations of 3D dimensional power Doppler indices and perinatal outcome in pregnancies complicated by intrauterine growth. International Journal of Gynecology & Obstetrics, 129(1), 5-8.

26) **Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS *et al.* (2008)** Evaluation of the effect of machine settings on quantitative three-dimensional power Doppler angiography: an in-vitro flow phantom experiment. Ultrasound Obstet Gynecol., 32: 551-559.

27) Pala HG, Artunc-Ulkumen B, Koyuncu FM *et al.* (2016): Three-dimensional ultrasonographic placental volume in gestational diabetes mellitus. J Matern Fetal Neonatal Med., 29(4): 610-4.

28) SalvesenDR, Higuras MT, Mansur CA, freeman J Brudenelle JM,Nicolaides KH (1993): Placental and fetal Doppler velocimetery in pregnancies complicated by maternal diabetes mellitus. AMJ Obstet gynecol., 168:645:652

29) Jauniaux E, Burton GJ (2006): Villous histomorphometry and placental bed biopsy investigation in Type I diabetic pregnancies. Placenta, 27: 468–74.

30) Hafner E, Metzenbauer M, Hoefinger D, Munkel M, Gassner R,Schuchter K *et al*. (2003): Placental growth from the first to the second trimester of pregnancy in SGA-fetuses and pre-eclamptic pregnancies compared to normal fetuses. Placenta, 24:336–342.

31) De Paula CF, Ruano R, Campos JA, Zugaib M (2008): Placental volumes measured by 3-dimensional ultrasonography in normal pregnancies from 12 to 40 weeks' gestation. J Ultrasound Med.,27:1583-90.

32) Odibo A O, Goetzinger K R, Huster KM *et al.* (2011): Placental volume and vascular flow assessed by 3D power Doppler and adverse pregnancy outcomes. Placenta, 32:230–4.

33) Martins WP, Raine-Fenning NJ, Ferriani RA *et al.* (2010): Quantitative three-dimensional power Doppler angiography: a flow-free phantom experiment to evaluate the relationship between color gain, depth and signal artifact. Ultrasound in Obstetrics & Gynecology, 35(3):361-8.

34) Odeh M, Ophir E, Maximovsky O *et al.* (2011): Placental volume and three-dimensional power Doppler analysis in prediction of pre-eclampsia and small for gestational age between Week 11 and 13 weeks and 6 days of gestation. Prenat Diagn**.,** 31:367–71.

35) Higgins M, Felle P, Mooney EE *et al.* (2011): Stereology of the placenta in type 1 and type 2 diabetes. Placenta, 32: 562–9.

36) Merce´ LT, Barco MJ, Bau S, Kupesic S and Kurjak A (2005*):* Assessment of placental vascularization by three-dimensional Power Doppler ‘‘vascular biopsy’’ in normal pregnancies. Croat Med J., 46:765–771.

37) Guiot C, Gaglioti P, Oberto M, Piccoli E, Rosato R, Todros T (2008): Is three-dimensional Power Doppler ultrasound useful in the assessment of placental perfusion in normal and growth restricted pregnancies? Ultrasound Obstet Gynecol., 31(2):171–176**.**

38) Yu CH, Chang CH, Ko HC, Chen WC, Chang FM (2003*):* Assessment of placental fractional moving blood volume using quantitative three dimensional power doppler ultrasound. Ultrasound Med Biol., 29:19-23.

39) Maly A, Goshen G, Sela J *et al.* (2005): Histomorphometric study of placental villi vascular volume in toxaemia and diabetes. Hum Pathol., 36: 1074–9.

40) Lai PK, Wang YA, Welsh AW (2010): Reproducibility of regional placental vascularity/ perfusion measurement using 3D Power Doppler Ultrasound. Obstet Gynecol., 36:202–209.

41) Negrini R, de Silva Bussamra LC, da Silva Vallada˜o de Freitas L, Araugo Ju"nior E, Piato S, Nardozza LM Moron AF, Aoki T (2010): Assessment of placental blood flow between 22 and 34 weeks of gestation by3D-Sonography Power Doppler vascular indices.Arch Gynecol Obstet., 284:53-57.