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Abstract: Objectives: Management of women with pre-gestational diabetes continues to be challenging for clinicians. This study aims to determine if 3D power Doppler (3DPD) analysis of placental volume and flow, and calculation of placental calcification using a novel software method, differ between pregnancies with type 1 or type 2 diabetes and normal controls, and if there is a relationship between these ultrasound placental parameters and clinical measures in diabetics.
Methods: This was a prospective cohort study of 50 women with diabetes and 250 controls (12-40 weeks gestation). 3DPD ultrasound was used to evaluate placental volume, vascularisation index (VI), flow index (FI) and vascularisation-flow index (VFI). Placental calcification was calculated by computer analysis. Results in diabetics were compared with control values, and correlated with early pregnancy HbA1c, Doppler results and placental histology.
Results: Placental calcification and volume increased with advancing gestation in pre-gestational diabetic placentae. Volume was also found to be significantly higher than in normal placentae. VI and VFI were significantly lower in diabetic pregnancies between 35 and 40 weeks gestation. A strong relationship was seen between a larger placental volume and both increasing umbilical artery pulsatility index and decreasing middle cerebral artery pulsatility index. FI was significantly lower in cases which had a booking HbA1c level ≥6.5%. Ultrasound assessed placental calcification was reduced with a histology finding of delayed villous maturation. No other correlation with placental histology was found.
Conclusions: This study shows a potential role for 3D placental evaluation, and computer analysis of calcification, in monitoring pre-gestational diabetic pregnancies.

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Novel placental ultrasound assessment: potential role in pre-gestational diabetic pregnancy

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ABSTRACT

Objectives: Management of women with pre-gestational diabetes continues to be challenging for clinicians. This study aims to determine if 3D power Doppler (3DPD) analysis of placental volume and flow, and calculation of placental calcification using a novel software method, differ between pregnancies with type 1 or type 2 diabetes and normal controls, and if there is a relationship between these ultrasound placental parameters and clinical measures in diabetics.

Methods: This was a prospective cohort study of 50 women with diabetes and 250 controls (12-40 weeks gestation). 3DPD ultrasound was used to evaluate placental volume, vascularisation index (VI), flow index (FI) and vascularisation-flow index (VFI). Placental calcification was calculated by computer analysis. Results in diabetics were compared with control values, and correlated with early pregnancy HbA1c, Doppler results and placental histology.

Results: Placental calcification and volume increased with advancing gestation in pre-gestational diabetic placentae. Volume was also found to be significantly higher than in normal placentae. VI and VFI were significantly lower in diabetic pregnancies between 35 and 40 weeks gestation. A strong relationship was seen between a larger placental volume and both increasing umbilical artery pulsatility index and decreasing middle cerebral artery pulsatility index. FI was significantly lower in cases which had a booking HbA1c level ≥6.5%. Ultrasound assessed placental calcification was reduced with a histology finding of delayed villous maturation. No other correlation with placental histology was found.

Conclusions: This study shows a potential role for 3D placental evaluation, and computer analysis of calcification, in monitoring pre-gestational diabetic pregnancies.

1. Introduction

Pre-gestational maternal diabetes, which complicates approximately 1% of all pregnancies is associated with an increased incidence of fetal morbidity and mortality [1]. Women with type 1 diabetes who have only a slightly raised HbA1c (an indicator of glycaemic control) in early pregnancy have been shown to have an increased risk of major fetal malformations [2]. Abnormalities in placental development and function may be a contributory factor to poor outcome, as diabetes compromises the placenta, independent of glycaemic control [3,4,5]. There is an increase in the size of the villous stroma and the diffusion distance within the maternal and fetal systemic circulations in the placenta affected by diabetes, with capillary volume also increased [6,7].

Delayed villous maturation (DVM) of the placenta is a condition which is strongly associated with maternal diabetes and an increased perinatal mortality rate [8] and can also be related to abnormal placental calcification [9]. Delayed villous maturation ranges from mild to severe in type, however regardless of severity the tertiary placental villi will be immature for gestational age. The most recent study, analysing clinical and ultrasound markers which may indicate the development of DVM, failed to demonstrate any associated findings on ultrasound [10]. Grannum grading, which is the only current method of assessing placental calcification, is felt by many clinicians to be unreliable and yet to date no other ultrasound method has been put forward as an alternative.

New ultrasound methods of placental assessment have been developed over the past decade or so [11]. One such method is three dimensional power Doppler (3DPD), which calculates volume, and blood flow according to three indices: vascularisation index (VI) or overall perfusion, flow index (FI) or blood flow intensity and vascularisation-flow index (VFI) or fractional moving blood volume. Recently a novel, 2D ultrasound imaging software tool, the 'placentometer' has been developed in the School of Medicine and Medical Sciences,

University College Dublin. The placentometer can be used off-line for calculating the percentage of placental calcification, and involves accurate identification of the placenta and repeatable measurement of the extent of calcification.

This study aims to determine if 3DPD ultrasound assessment of placental volume and vascularity and computer analysis of placental calcification, using the placentometer, differ between pregnancies complicated with type 1 and type 2 diabetes and normal. This study also aims to determine if there is a relationship between these placental parameters, and glycaemic control, Doppler and placental histology results.

2. Material and methods

2.1 Patients

This was a prospective cohort study. With institutional ethical approval and maternal written consent thirty seven women with type 1 diabetes mellitus (T1DM) and thirteen women with type 2 diabetes mellitus (T2DM) were recruited to the study. Gestational age at the time of the scan ranged from 12+2 to 39+5 weeks. All scans were performed transabdominally using a Voluson 730 Expert ultrasound machine (GE Medical Systems, Austria), equipped with curved array transducers. A 2 to 7MHz transducer was used to acquire all two dimensional (2D) images, and a 4 to 8 MHz transducer was used to acquire the three dimensional (3D) images. The number of scans per patient depended on the gestational age at the time of recruitment, and ranged from one to six. Each scan incorporated assessment of placental site, fetal biometry and estimation of fetal weight (after 30 weeks gestation), Doppler studies of the umbilical artery (UA), middle cerebral artery (MCA) and uterine artery (UtA) were performed, with the pulsatility index (PI) calculated.

2.2 3DPD placental analysis

A 3DPD placental image was saved at each scan with subsequent analysis of images to calculate volume, VI, FI and VFI flow using the Virtual Organ Computer-aided AnaLysis (VOCAL^{TM}) software (3 dimensional Sonoview, GE Healthcare). The method for saving and analysing images has been previously described [12]. Once each image was rotated 180^{O} a shell contour was displayed in the lower right hand corner of the display, and the volume automatically calculated. Fig. 1 displays a volume of 371.709 cm^3.

Once the contour was accepted as correct the vascular indices VI, FI and VFI were calculated.

2.3 Calculation of placental calcification

The initial step in calculating the percentage of placental calcification, using the placentometer, was to select the region of interest (ROI), by drawing an outline around the placenta using a pointing device controlled by the mouse. The pixels were recorded following the mouse movements, were then joined into line-segments and these segments were finally combined to form a continuous outline. The ROI included the basal, body and surface areas of the placenta. A slider was then used to alter the intensity threshold for defining calcification within the ROI. A flood-filing algorithm then created a secondary reference map that is used in a quantification algorithm. Once satisfied that all the relevant areas of calcification were highlighted metric analysis was applied by selecting the 'Quantify' function. An output metric was then produced in the form of pixel counts and the overall percentage of calcification in reference to the total number of pixels within the ROI (Fig. 2).

.3 Placental examination All placentae were submitted to the laboratory for full histological examination. The weight of the trimmed, fresh placental disk was recorded on a calibrated laboratory sales following removal of the cord, membrane and fresh blood.

3. Statistical analysis

All relationships between placental ultrasound parameters and clinical outcomes are given for the diabetic group only. The normal group was used as a comparison and to define levels of individual parameters, adjusted for gestational age. Statistical analysis was performed using PASW statistics, Version 18 (SPSS Inc., Chicago, IL, USA). T1DM and T2DM cases are combined for the purpose of statistical analysis. Linear regression analysis was conducted to determine the relationship between the placental study parameters and gestational age. 3DPD and calcification calculations were analysed for both changes with gestational age within the diabetic group and for comparisons with previously defined normal values. Gestational age was taken as ranging from 12 to 40 weeks, and was also divided into four categories of 10-20 weeks, 20-30 weeks, 30-35 weeks and 35-40 weeks. The study parameters (normal values) were correlated with Doppler results and values from the final scan performed (between 35 and 40 weeks gestation) correlated with the maternal booking HbA1c (a level of < 6.5% taken to indicate good control), and histology results. Pearson's Chi-square and independent samples t-tests were used to assess statistical significance for relationships between parameters and histology. The percentage of placental calcification, as defined by computer analysis, was logarithm transformed to achieve normal distribution. Independent samples t-tests, and one-way ANOVA were both used to compare mean values between two and more than two different groups respectively. $P<0.05$ was considered statistically significant.

4. Results

The clinical characteristics of participants are displayed in Table 1.

A total of 155 scans were performed (an average of 3 scans per patient). In 6 cases it was not possible to obtain an adequate 3DPD image of the placenta for the purpose of calculating volume, and vascularity. Values for these variables are therefore available for 149 scans. A suitable image for software analysis to calculate the percentage of calcification was obtained for 152 scans.

4.1 Placental volume

Placental volume ranged from 38.42cm^3 to 694.47cm^3 and had a mean of 249.04cm^3 (SD 132.42). Volume was found to be significantly correlated with gestational age over the range of all scans performed, with an increase of 1.13cm^3 per day of gestational age increase (p<0.001). Comparison of placental volume between the diabetic and previously defined normal values, showed that placentas of diabetic mothers had a significantly larger volume across the range of gestational age (p< 0.001), and within the gestational age groups from 20 weeks gestation.

The values of placental volume in the diabetic group were plotted on a centile chart, using the normal 5th, 50th and 95th centile value trends (based on regression line) from 12+6 to 40 weeks gestation (Figure 3). The larger placental volume in the diabetic group of patients compared to normal can be seen mainly in the 30-35 and 35-40 gestational age groups. As Figure 3 demonstrates, no values plot below the 5th centile, the majority of values plot between the 50th and 95th centile, and eleven values plot over the 95th centile, between 30 and 40 weeks gestation.

4.2 Placental VI, FI and VFI

In diabetic placentae VI ranged from 3.50 to 35.23, with a mean of 15.78 (SD 6.22). FI ranged from 33.45 to 60.67, with a mean of 47.91 (SD 5.69) and VFI ranged from 1.32 to 19.16, with a mean of 7.72 (SD 3.37). The values of the 3 indices were found to be independent of gestational age. Comparison between the diabetic and normal values showed that placentas of diabetic mothers had a significantly lower (p=0.05) vascularisation index between 35 and 40 weeks gestation (mean VI diabetic 15.35 (SD 6.13; mean VI normal 17.47 (SD 7.12)).

The FI was significantly lower in diabetic placentas at both 30-35 (p=0.042) and 35-40 weeks (p=0.016) gestation. From 30-35 weeks the mean diabetic FI was 47.81 (SD 4.94) and the normal FI was 49.86 (SD 5.98). The diabetic FI was 47.25 (SD 5.47) from 35-40 weeks, and the normal value was 49.39 (SD 5.98). The FI was found to decrease significantly as the volume increased (FI=51.502 – (0.015 x volume)), with a p value of <0.001. As with the VI the difference between diabetic and normal placental VFI was from 35 weeks gestation, with the diabetic VFI significantly (p=0.023) lower (mean VFI diabetic 7.40 (SD 3.25; mean VFI normal 8.74 (SD 3.88)). The differences in the values of VI, FI and VFI between diabetic and normal placentae are shown in Table 2.

4.3 Placental calcification

The percentage of placental calcification, as defined by the placentometer, ranged from 0.00 to 22.36% with a mean of 3.11% (SD 4.15), and was found to be significantly correlated (p<0.001) with gestational age over the range of scans performed. Overall placental calcification was higher in the diabetic than the normal group (p=0.005), however this is most likely due to the higher number of scans performed within the normal category at an earlier gestational age (normal n=90, diabetic n=24, before 30 weeks) as this was not apparent when broken down into gestational age categories.

4.4 Relationship with glycaemic control, Doppler and histology results

Forty patients (80%)) had poor glycaemic control (HbA1c ≥ 6.5%) at booking, with 20% (n=10) having good glycaemic control. Table 3 shows the mean values of the placental parameters at 35-40 weeks gestation in relation to the booking HbA1c value. The flow index was significantly lower (p=0.047) in those cases which had a booking HbA1c level of ≥6.5%.

The mean booking HbA1c for the total group of diabetic patients was 7.26%. The percentage of calcification was higher in cases where booking HbA1c was ≥7%; <7% 4.02% (SD 5.36), ≥7% 6.42% (SD 5.04), although not quite reaching significant levels (p=0.055). A percentage of calcification greater than the 50th centile (normal value) between 35 and 40 weeks, correlated significantly (p=0.013) with a higher mean HbA1c at booking, i.e. 7.64% as opposed to 6.75% where calcification was less than the 50th centile.

Analysis found that there was an association between an increasing placental volume and an increasing UA PI between 12 and 40 weeks gestation (p=0.035). Dividing scan results into gestational age week groups showed that the lower the MCA PI, the higher the placental volume between 20 and 35 weeks (20-30 weeks: p=0.005; 30-35 weeks: p=0.008).

Placental parameters at the last scan performed for each patient were correlated with the placental histology for the 46 cases in the diabetic group of women who delivered after 37 weeks. Volume and vascularisation were not available for 1 case. 32 cases had pathology present (DVM n=9, accelerated maturation n=13, mixed maturation n=7 and chorangiosis n=12). 9 cases of chorangiosis had a co-existing maturation defect (delayed x 3, accelerated x 3 and mixed. Six out of the 9 cases of DVM had a percentage of calcification < normal median for their gestational age, as opposed to 11 of the 37 cases without delayed maturation (P=0.011). The mean percentage of calcification, as defined by the placentometer, was also

reduced (p=0.022) at between 35 and 40 weeks in cases of DVM (mean calcification percentage DVM 2.10 (SD 0.88); mean calcification without DVM 6.69 (SD 5.98)).

5. Discussion

The results of this study show that placental volume is correlated with gestational age in type 1 and type 2 diabetic pregnancies, increasing as gestation advances. Placental volume was found to be significantly larger in diabetic patients when compared with normal values. The volume was found to be significantly larger at all stages of gestation from 12 weeks, the difference being greatest after 30 weeks gestation (this may be due to the higher number of cases in both groups at this gestation). A previous study found no difference in placental volume between the placentae of diabetic and non-diabetic pregnancies, however their estimation of volume was at stereology and was based on weight calculations [7].

There were some interesting comparisons between diabetic and normal pregnancies in relation to the differences in vascularisation and blood flow. The vascularisation index was significantly lower in diabetic pregnancies between 35 and 40 weeks gestation and the flow index was lower in diabetic placentas after 30 weeks gestation This may be explained by the fact that diabetes is associated with microvascular disease, resulting in a reduction in placental blood flow. The increased villous stroma and diffusion distance between fetal and maternal circulations results in an increase in the number of fetal vessels and subsequently lead to a reduction in the blood flow, characterised by the lower flow index (FI) found in the diabetic group. Linear regression also demonstrated a decrease in the flow index in relation to an increase in placental volume (p<0.001). This has also been seen previously in normal pregnancies [12]. The vascularisation-flow index was also significantly lower in diabetic placentae (than normal) between 35 and 40 weeks gestation. The results of the software analysis of calcification are very encouraging as they show that the percentage of

calcification, defined by the placentometer, increased as gestation advanced. Whilst placental calcification was higher in diabetic than normal placentae overall, this was not the case when broken down into the gestational age categories. As suggested previously this is most likely explained by the difference in the number of scans within the normal category at an earlier gestational age.

Current guidelines recommend that early pregnancy HbA1c levels, for women with Type 1 and Type diabetes, should be as low as possible [13]. The mean FI was significantly lower between 35 and 40 weeks gestation where there was evidence of poor glycaemic control at booking. It has been demonstrated that differences in HbA1c levels at best predict 23% of birth weight differences [14]. However a recent study did show an increase in capillary volume in those pregnancies with a high booking HbA1c level, which, while not significant, would explain the lower flow index in our study [7]. The mean HbA1c at booking was significantly higher however, demonstrating poor glycaemic control, in cases where the percentage of calcification was above the 50th centile (normal ranges) for gestational age .

Our study showed a relationship between a higher placental volume, which can be a sign of fetal hypoxia in diabetic patients, and both an increased UA PI and decreased MCA PI. This study found no significant relationship between placental volume, vascularisation or blood flow and placental pathology. We did though find that placental calcification was reduced significantly (ie $<50^{th}$ centile for gestational age) in two thirds of the cases of delayed villous maturation. This is in keeping with previous studies which evaluated calcification using Grannum grading, which found lower Grannum grades in cases of delayed maturation [9, 15].

Whilst there have been major improvements in recent years in the management of diabetic pregnancies they still remain a high risk group. The rate of pre-gestational diabetes is increasing, as a result of the increase in the rate of T2DM in the general population [16]. A possible role for 3D evaluation of placental volume in the first half of pregnancy in the

prediction of macrosomia has already been suggested [17]. To our knowledge this is the first study comparing 3D evaluation of the placenta between normal and diabetic pregnancies throughout the second and third trimester of pregnancy. Whilst we acknowledge that further research is required the results of this study indicate that there may be a role for 3D power Doppler evaluation of placental volume, vascularisation and blood flow combined with computer analysis of calcification in the monitoring and subsequent management of diabetic pregnancies.

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Figure Legend 1

Fig. 1. 3D placental volume displayed as 371.709 cm^3

Figure Legend 2

Fig. 2. Placental outline as defined manually using the placentometer on the left and definition of the placenta, with the higher intensity areas (representing calcification) highlighted in green on the right (38+1 weeks gestation.
[The output metric indicates that 7985 pixels out of a possible 65192 are highlighted and that the overall percentage of calcification is 12.1484%]

Figure Legend 3

Fig.3. Diabetic (type 1 and 2) placental volume plotted against normal 5^{th}, 50^{th} and 95^{th} centile value trends

Table 1
Clinical characteristics of participants: women with pre-gestational diabetes mellitus

Clinical characteristics	n (range/%)
Maternal age	33 (21-45)
Parity (% primiparous)	24/50 (48%)
Gestational age at delivery (weeks + days)	38+2 (34+0 - 41+1)
Birth weight (g)	3481 (2630 – 4900)
Placental weight (g)	512 (259 – 776)
Apgars < 7 at 1 min	0
Apgars < 7 at 5 min	0
Type of delivery	
Normal vaginal	22
Instrumental	4
LSCS	24
Cord pH < 7.2	9
Gender (% female)	28/50 (52%)
Admission to NICU	4/50 (8%)

NICU: neonatal intensive care unit

Table 2

Comparison of mean placental vascularisation index (VI), flow index (FI) and vascularisation-flow index (VFI) between type 1 and 2 diabetics and normal pregnancies (35-40 weeks gestation)

Placental Blood Flow	Diabetic Mean (SD)	Normal Mean (SD)	*P* value
VI	15.35 (6.13) (n=72)	17.47 (7.12) (n=84)	0.050
FI	47.25 (5.47) (n=72)	49.39 (5.98) (n=84)	0.016
VFI	7.40 (3.25) (n=72)	8.74 (3.88) (n=84)	0.023

Table 3

Mean placental volume, vascularisation and calcification % at 35-40 weeks in relation to glycaemic control at booking

HbA1c (n)	Volume Mean (SD)	VI Mean (SD)	FI Mean (SD)	VFI Mean (SD)	Calcification% Mean (SD)
<6.5%	236.86	17.79	49.86	8.86	3.55
(n=10)	(91.92)	(6.95)	(5.45)	(3.27)	(3.06)
≥6.5%	286.68	15.11	45.83	7.12	5.96
(n=40)	(129.76)	(6.42)	(5.14)	(3.42)	(5.62)
P value	0.290	0.283	0.047*	0.183	0.458

[VI: vascularisation index; FI: flow index; VFI: vascularisation-flow index] *$p < 0.05$

Figure 1

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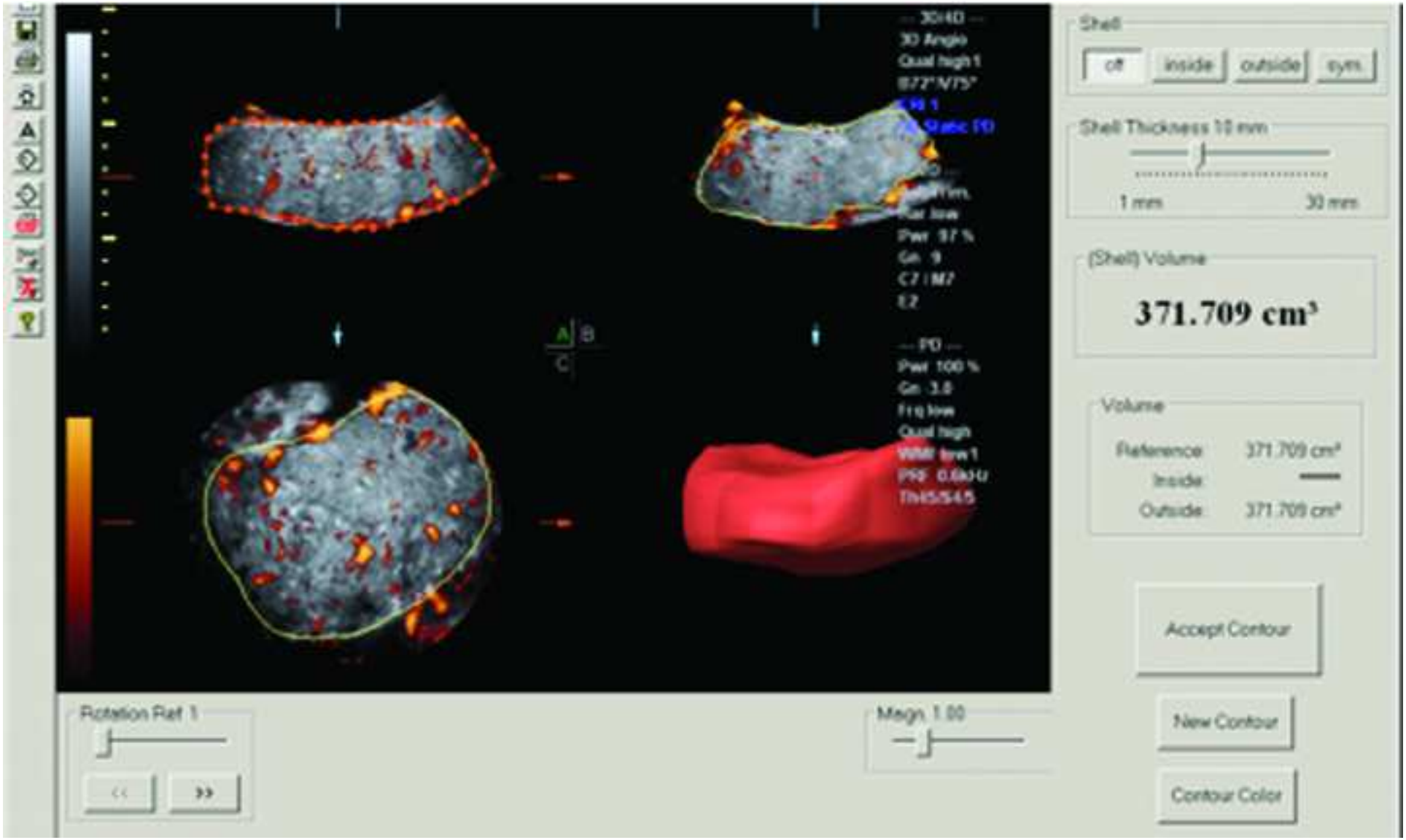

Figure 2

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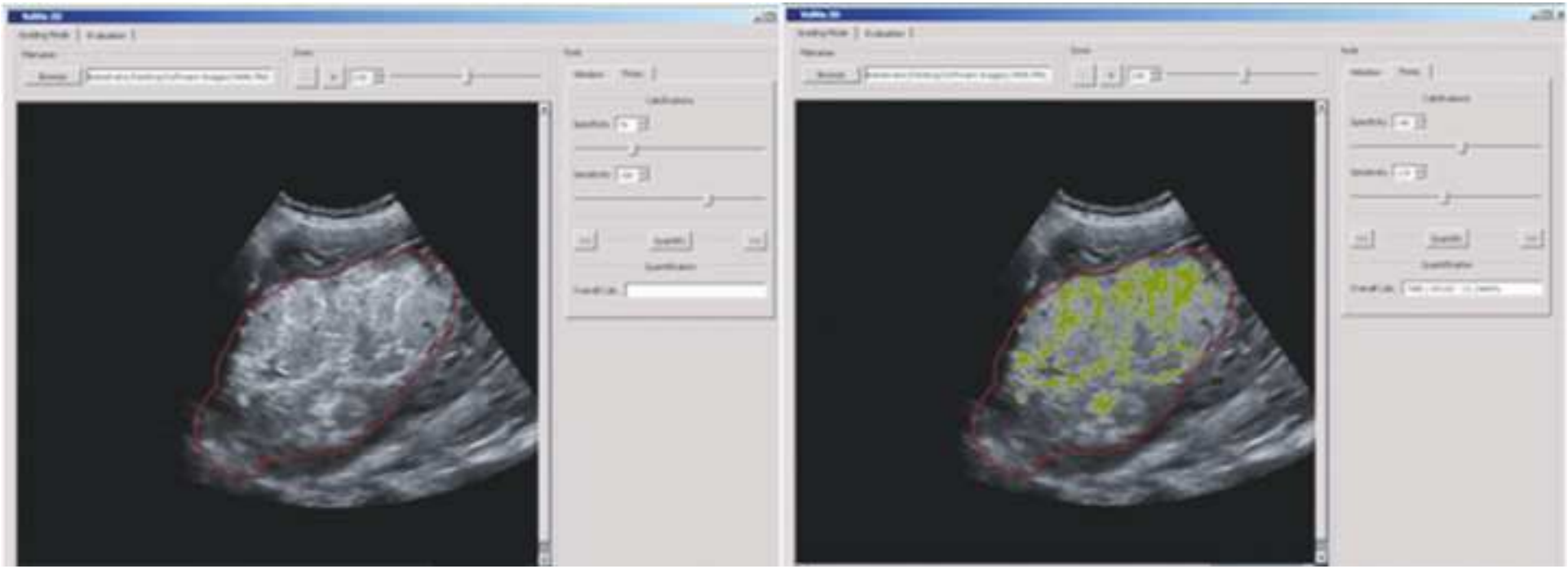

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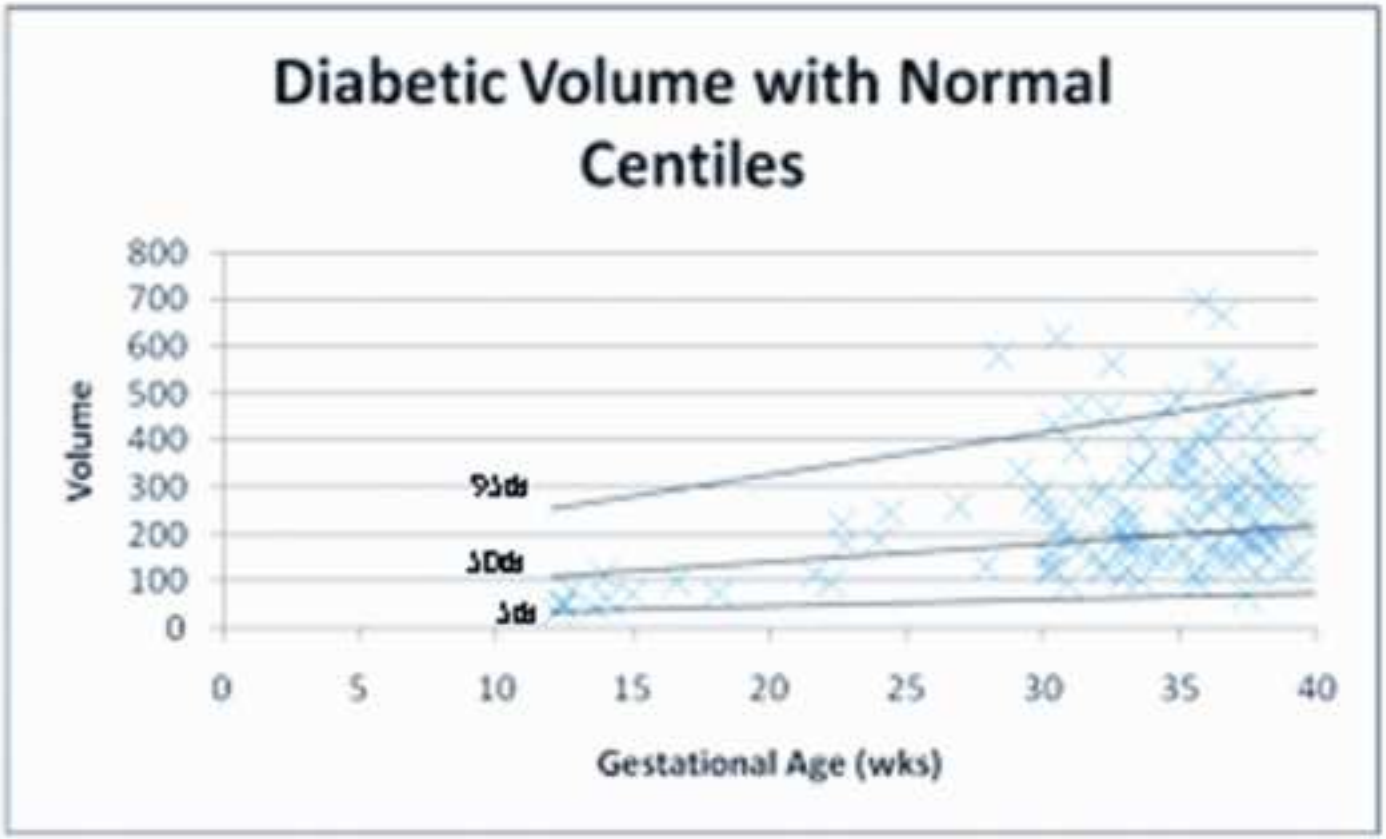

Fig 4. Diabetic (type 1 and 2) placental volume plotted against normal 5th, 50th and 95th centile value trends