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Applications of Doppler Studies for Fetal Surveillance in Diabetic Pregnancies

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1. Introduction

Diabetes mellitus complicating pregnancy is one of the most common antenatal complications that are associated with significant perinatal mortality and morbidity (Magee et al., 1993; Platt et al., 2002; Schmidt et al., 2001). Diabetic pregnancies can be divided into two categories: those with pre-gestational or pre-existing diabetes mellitus in which the diagnosis is made in the pre-pregnancy state, and those with gestational diabetes mellitus (GDM). Pre-existing diabetes consists of type I (insulin-dependent) diabetes mellitus (IDDM)with an incidence of around 0.5%, and type 2 (non-insulin-dependent) diabetes with an incidence of 2-3% (Kapoor et al., 2007). The incidence of gestational diabetes mellitus differs in different populations (Gunton et al., 2001) and ethnic groups, and was shown to be as high as 13% in Chinese populations (Ko et al., 2002). Effective treatment of pre-existing as well as gestational diabetes mellitus was shown to improve outcome and reduce perinatal mortality, as compared to untreated patients (Lao et al., 2001; Langer et al., 2005).

The pathological conditions encountered in fetuses of diabetic pregnancies differ in those with pre-existing diabetes mellitus and those with gestational diabetes. Pre-existing diabetics with persistent hyperglycaemia in the perinatal period are at higher risks of congenital malformations (Reece et al., 2007). In addition, those women with long-standing pre-existing diabetes before the index pregnancy run a higher risk of having diabetic vasculopathy that may affect various organ-systems in the body. Involvement of the uterine arteries will affect the development of an effective utero-placenta blood flow, which would be vital in maintaining normal growth and development in the fetus. The clinical manifestation of fetal growth restriction (also called intrauterine growth restriction) is thus more common in these pregnancies. The presence of significant congenital abnormalities and severe fetal growth restriction resulting from such conditions are logically directly related to increase in perinatal mortality and morbidity. On the other hand, gestational diabetes is usually only diagnosable either in a screening protocol or from clinical risk factors, by oral glucose tolerance test from mid trimester onwards, due to the effects of diabetogenic hormones from the placenta. The carbohydrate intolerance is thus short-lived and should last only from mid trimester to term. The hyperglycaemic states of the diabetes should revert to normal shortly after delivery with the removal of the placenta. Thus, chronic complications such as vasculopathy in the pregnant women will not have time to evolve during the course of pregnancy. On the contrary, the diabetic hyperglycaemic states

in gestational diabetes would stimulate fetal hyperinsulinemia, which would in turn lead to over-secretion of insulin-like growth factors (IGF), leading to overgrowth of the fetus (Kapoor et al., 2007). Thus, in contrast to pre-gestational diabetes mellitus, where vasculopathy is rife and the incidences of pre-eclampsia and fetal growth restriction are commonly encountered, GDM pregnancies pose a different category of pathophysiology and clinical risks. The most common fetal problems for gestational diabetes will be macrosomia with associated polyhydramnios, as well as increased risks of near term stillbirths and neonatal metabolic complications in livebirths (Sacks, 2007). Indeed, recent data borne out by the HAPO study has demonstrated that in maternal hyperglycaemic states less severe than in diabetes mellitus is also associated with increased risks of adverse pregnancy outcomes (HAPO Study Cooperative Research Group, 2008)

A lot of emphasis has been put on fetal surveillance in these high-risk pregnancies in the attempt to optimise pregnancy outcome. There is, however, no consensus as to the best methods of antepartum surveillance (American College of Obstetricians & Gynecologists, 2001). The use of Doppler studies of the umbilical artery has been demonstrated to reduce perinatal adverse outcome in non-diabetic pregnancies (Alfirevic et al., 1995), but its use in diabetic pregnancies have shown conflicting results. While umbilical artery Doppler studies have been shown to be more predictive of adverse outcome than cardiotocography and biophysical profile in diabetic pregnancies (Bracero et al., 1996), fetal compromise would occasionally still be observed despite normal Doppler studies (Johnstone et al., 1992). Thus, the precise value of Doppler studies in the monitoring of GDM pregnancies remains controversial.

2. Serial growth scans for diabetic pregnancies

The recommendations for diagnosis and treatment of GDM of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (Metzger et al., 2007) suggest consideration of fetal growth patterns to guide metabolic management of pregnant women with GDM. However, estimation of fetal weight, particularly at term and in fetuses with high neonatal weight, is not as precise as desirable (Sacks et al, 2000). Fetal overgrowth and accelerated growth velocity of the abdominal circumference in the third trimester is known to predict large for gestational age babies (Kehl et al., 1996). Fetal overgrowth with macrosomia and associated polyhydramnios is associated with higher risks of near term stillbirth, as well as various neonatal metabolic derangements, including neonatal hypoglycaemia, electrolyte disturbances and neonatal jaundice. Previous randomized studies have demonstrated that measurement of fetal abdominal circumference throughout pregnancy in women with GDM is useful to identify pregnancies at high risk for fetal overgrowth and thus in need of more vigilant treatment including insulin therapy (Bonomo et al., 2004).

Serial measurements of the fetal abdominal circumference have been used to guide metabolic management of pregnancies complicated by gestational diabetes mellitus. There is at present no consensus as to the optimal protocol for such growth scans. A recent study evaluated the number of sonograms needed to reliably predict the absence of fetal overgrowth in GDM pregnancies. A total of 4478 ultrasound examinations were performed on 1914 subjects. Of 518 women with fetal abdominal circumference > 90th percentile, the diagnosis was detected in 73.9% with the first ultrasound examination at entry and in 13.1% with the second ultrasound examination. Of the fetuses, 85.9 and 86.9% of the fetuses were

born non-large- for- gestational- age when abdominal circumference was < 90th percentile at 24-27 weeks and 28-32 weeks respectively; and 88% were born non-large-for-gestational-age when both scans showed normal growth. For those women who had no risk factors for fetal overgrowth, such as body mass index > 30 kg/m², history of macrosomia, and fasting glucose > 100 mg/dl, the accuracy of prediction of a non-large-for-gestational-age neonate was 90.0, 89.5 and 95.2%. The predictive ability did not increase with more than two normal scans. It was concluded that the yield of sonographic diagnosis of a large fetus dropped markedly after the finding if a large fetal abdominal circumference < 90th percentile on tow sonograms, which excludes with a high reliability the risk of a large for gestational age newborn. The ability was enhanced in women who had no risk factors for neonatal macrosomia (Schaefer-Graf et al., 2011). Thus, sonographic evaluation of fetal growth parameters is a crucial part of ultrasound assessment of diabetic pregnancies. The application of Doppler examination should take into account the data from such growth assessment parameters.

3. Use of Doppler studies for fetal surveillance

Various Doppler parameters have conventionally been utilized for fetal surveillance. The use maternal uterine artery Doppler as a screening tool to predict subsequent development of pre-eclampsia and fetal growth restriction in later gestation have gained acceptance in recent years. Umbilical artery Doppler, middle cerebral artery Doppler, or the combination of the two to produce a cerebral-placental ratio, have been widely used for the assessment of growth restricted fetuses. Less commonly used arterial Doppler parameters include fetal thoracic aorta or renal arteries. Venous Doppler assessment has been extensively investigated in recent years, including umbilical venous waveforms, intrahepatic venous Doppler and ductus venosus Doppler. The following sections attempt to review the application of the more commonly used Doppler parameters in diabetic pregnancies.

3.1 Maternal uterine artery

Maternal uterine artery remodelling is the hallmark sign of successful placentation, which can be demonstrated by progressive alterations in Doppler waveforms derived from the immediate extrauterine portion of the uterine artery. Pre-pregnancy uterine arteries show high resistance and elastic recoil in the form of early diastolic notches and low diastolic flow (Schulman et al., 1986). Successful placental invasion removes intimal muscle and reduces vascular resistance and elastic properties, giving more rigorous diastolic flow. In pregnancies with normal placentation, Doppler studies show that this remodelling is rapid, with loss of notching by 12 weeks and low resistance indices by 20 weeks or sooner. When placentation is deficient, notching of waveforms remains with high resistance (Papageorhiou et al., 2001). Such a picture of deficient placentation strongly predicts maternal hypertension, including proteinuric pre-eclampsia, fetal growth restriction and fetal demise (Coleman et al., 2000). Uterine artery Doppler screening using high resistance, persistent notching, or both, identifies such risks with a sensitivity up to 85% for severe proteinuric pre-eclampsia and for severe fetal growth restriction (Papageorghiou et al., 2002). However, there is so far no well established evidence of using such screening for adverse outcomes for either pre-existing or gestational diabetes mellitus alone.

When uterine artery Doppler were examined in a cohort of 43 pregnancies complicated by insulin-dependent diabetes, it was found that the uterine artery resistance indices were

slightly higher in the presence of evident morphological vasculopathy, but could not predict diabetic specific fetal morbidity. It was concluded that in patients with diabetic vasculopathy, the uterine artery was also affected, but there was no relationship with long or short term parameters of glycaemic control. Based on the data, it was concluded that Doppler flow velocimetry of the uterine artery was a poor predictor of diabetes-specific fetal morbidity (Zimmermann et al., 1994).

In another prospective survey, 24 well controlled insulin dependent pregestational diabetic pregnancies were compared with 25 healthy pregnant women and Doppler ultrasound was performed on two occasions in the third trimester separated by a one-month interval. At the first examination, the median pulsatility index in the fetal thoracic aorta and in the uterine artery was significantly lower in the diabetic group as compared to healthy controls, whereas umbilical and uterine pulsatility indices were similar. At the second examination at a more advanced gestation, a significant physiological decrease in the median pulsatility index of the fetal aorta and uterine artery was observed in the controls, but not in the diabetic group. There was no correlation between the glycosylated haemoglobin or random blood glucose levels and the Doppler indices. An increased incidence of neonatal morbidity was noted in the diabetic group. Thus, the normal physiological third trimester fall in resistance indices in the uteroplacental and fetal placental indices was apparently absent in the diabetic group, and this was associated with increased neonatal morbidity. The pulsatility indices were not influenced by blood glucose regulation (Grunewald et al., 1996).

A similar retrospective study of 155 pre-gestational diabetic women between 22 weeks gestation and term also found that abnormal uterine artery Doppler with increased pulsatility index was related to pre-existing diabetic states with vasculopathy and adverse pregnancy outcome. There was an increased incidence of abnormal umbilical artery Doppler in those with abnormal uterine artery Doppler, indicating that the vasculopathy might influence placental perfusion and fetal well-being (Pietryga et al., 2006). Therefore, it is logical to expect that such screening by uterine artery Doppler will likely be effective only if the diabetic pregnancy is also complicated by gestational hypertension or fetal growth restriction. Given the higher incidence of such obstetric complications in pre-existing diabetes mellitus as compared to GDM, screening of diabetic pregnancies using uterine artery Doppler in mid trimester would probably produce a higher yield in the former group.

3.2 Fetal umbilical artery Doppler

The use of Doppler studies of the umbilical artery has been demonstrated to reduce perinatal adverse outcome in non-diabetic pregnancies (Alfirevic et al.,1995), but its use in diabetic pregnancies have shown conflicting results. Umbilical artery angle independent indices (systolic/diastolic ratio or pulsatility index) decrease with advancing gestation because of decreases in placenta vascular resistance, which physiologically occurs with advancing gestation. In pathologic conditions, such as intrauterine/ fetal growth restriction, the umbilical artery waveform change and the angle-independent indices become abnormal, giving values above their reference ranges. End-diastolic velocity may thus change from normal to reduced, absent or reversed. These changes represent an increased placental vascular resistance, and could pathologically be associated with a decrease in the number of placental arteries per high power field (Giles et al., 1985). The most common scenario for fetal growth restriction include placental insufficiency in singleton or multiple pregnancies from various aetiologies, which may or may not be associated with pre-eclampsia or other maternal conditions, or in fetuses with congenital malformations. Such a picture commonly

occurs in women with pre-existing diabetes mellitus with vasculopathy. In pregnancies with suspected fetal growth restriction, the use of umbilical artery Doppler has been demonstrated to reduce the number of perinatal deaths and unnecessary obstetric interventions. In the context of diabetic pregnancies, however, the applications of umbilical artery Doppler remain controversial.

To investigate the vascular resistance by Doppler ultrasound in the umbilical artery of 53 IDDM pregnancies longitudinally over the course of pregnancy, the resistance index of the Doppler waveform was correlated with the mean value of a 24 hour blood glucose profile and the concentrations of glycosylated haemoglobin (HbA1C), which represented parameters of metabolic control. Regression analysis, however, showed no significant correlation between vascular resistance and mean blood glucose levels or HbA1C concentrations (Zimmermann et al., 1992).

In another study that included 67 normotensive women with pregnancies complicated by IDDM, the umbilical artery pulsatility index was compared with both pregnancy complications and perinatal outcome. The last umbilical pulsatility index value before delivery was used for analysis, and Doppler results were not used for patient management. Out of this cohort, 44 (66%) had pulsatility index values within the normal range between the 5th to 95th percentile, while 23 (34%) had abnormally high pulsatility index values. Among the group with pathologically abnormal umbilical pulsatility indices, analysis of the data revealed a significantly higher incidence of both caesarean section for acute fetal distress and perinatal complications. These complications include respiratory distress syndrome, hyperbilirubinemia, neonatal hypoglycaemia, and the need for neonatal intensive care unit admission. The authors concluded that in at least one third of IDDM patients, increased vascular resistance in the umbilical arteries were found, and these also suffered from higher incidences of perinatal complications (Fadda et al., 2001).

A retrospective study of 146 patients with gestational diabetes noted that Doppler examination of the umbilical arteries seemed to be of little clinical value unless pregnancy was complicated by pre-eclampsia or intrauterine growth restriction. The study included 227 patients with diabetes, and umbilical artery Doppler velocimetry and glycaemic control were examined in the third trimester. An elevated systolic/diastolic ratio and an abnormal glycosylated haemoglobin level were associated with adverse pregnancy outcome, but there was no stratification for vascular disease or fetal growth restriction in the data (Bracero et al., 1996).

In a prospective study of 65 well controlled diabetic pregnancies, Doppler measurements of uterine arteries, umbilical artery, the fetal descending thoracic aorta, and the middle cerebral artery (MCA) were performed together with cordocentesis for measurement of umbilical venous blood pH, pO2 and haematocrit. It was found that the mean umbilical venous blood pH was significantly lower and the haematocrit significantly higher than the appropriate normal mean for gestation for these diabetic pregnancies. However, the Doppler indices of the placental and fetal circulations were essentially normal, except in some of the cases complicated by pre-eclampsia or intrauterine growth restriction (Salvesen et al., 1993). It was thus concluded that maternal diabetes mellitus was not associated with abnormalities in Doppler indices of the placental or fetal circulations.

To evaluate a random single Doppler study of the systolic/diastolic ratio of the umbilical artery as a predictor of perinatal outcome in diabetic pregnancies, a prospective double-blind study was performed in 92 diabetic pregnancies between 28 and 40 weeks gestation, and the results were associated with perinatal outcome parameters. The sensitivity and specificity of the Doppler studies as a predictor of poor perinatal outcome were 39% and

92% respectively. The positive and negative predictive values were 54% and 86% respectively. The authors suggested that the systolic/diastolic ratio of the umbilical artery offer no advantage over other well established tests in management of diabetic pregnancies (Ben-Ami et al., 1995).

In a cohort of 104 women with both type I and type II pre-existing diabetes mellitus, umbilical artery Doppler was performed at 28, 32, 36 and 38 weeks gestation. Overall, 22% had an elevated pulsatility index. If the Doppler examination was carried out within 2 weeks of delivery, 71% with abnormal umbilical artery Doppler had adverse perinatal outcome (likelihood ratio 4.2). However, the sensitivity of umbilical artery Doppler to predict such adverse outcome was only 35%, while specificity was 94%. The positive Predictive value was 80% and negative predictive value was 68%. Only 30% of women with adverse perinatal outcome had abnormal umbilical artery Doppler measurements. The authors thus concluded that the performance of umbilical artery Doppler was not satisfactory even in this group of high risk women with pre-existing diabetes, and that it was not a good predictor of adverse perinatal outcome (Wong et al., 2003).

To investigate whether complications were higher in diabetic pregnancies with cardiac maladaptation, fetal, uteroplacental and echocardiographic examinations were compared in the second and third trimester between diabetic and healthy pregnant women. Physiological cardiac hypertrophy was found in healthy women but was less prominent in patients with diabetes. While the majority of patients studied have normal Doppler results, the abnormal uteroplacental flow group consisted entirely of women with pregestational diabetes, especially IDDM patients. Neonatal complications were also more common in this subgroup. No relationship was found between echocardiographic findings, Doppler waveforms and perinatal outcome. Similar to previous studies, the findings confirmed that umbilical and uteroplacental Doppler were useful only in pre-existing diabetes, but not in GDM patients (Parlakgumus et al., 2010).

From the above studies, it can be seen that both observational data and randomized control data have failed to show any consistent association between maternal diabetes and abnormal umbilical artery Doppler indices. It is apparent that the current evidence supports the use of umbilical artery Doppler only in those patients with diabetes who have pregnancies complicated by hypertensive diseases, fetal growth restriction, or vasculopathy. Umbilical Doppler studies cannot be recommended as a routine screening for fetal surveillance especially in patients without pre-existing diabetes mellitus (Pietryga et al., 2006).

3.3 Middle cerebral artery Doppler

The middle cerebral artery (MCA) is the most studied cerebral artery because it is simple to sample, consistent and reproducible, and provides information on the cerebral blood flow in normal and growth restricted fetuses (Mari et al., 2008). In addition, the MCA can be sampled at an angle of near zero degrees between the ultrasound beam and the direction of the blood flow, so that the genuine velocity of the blood flow can be measured. In growth restricted foetuses, there is a redistribution of the blood flow from the fetal periphery to the brain, commonly known as the brain-sparing effect. In severe fetal growth restriction with abnormal umbilical artery, MCA Doppler is a valuable adjunct, with abnormal findings signifying the onset of compromise that should soon require delivery (Dubiel et al, 2002).Overt MCA changes appear as increased diastolic velocity, and an altered cerebral-placental ratio will thus be observed. Changes in cerebral-placental ratio may be at least

partly pressure-dependent, reflecting structural placental deficiencies, whereas brain-sparing is attributed to hypoxia induced cerebrovascular dilatation (Baschat, 2003). In those pregnancies over 34 weeks gestation, placental functional decline may be more dominant that structural decline. Thus MCA changes in brain-sparing may appear in small fetuses with near-normal umbilical artery Doppler (Severi et al., 2002; To et al., 2005). Such findings are again more likely to occur in women with pre-existing diabetes mellitus with vasculopathy than in those with gestational diabetes mellitus.

Another use for examining the MCA is to detect fetal anaemia. The MCA can be insonated at an angle between zero and 15 degrees to measure the actual flow velocity in the vessel. The lowest intra- and inter-observer variability is obtained when the MCA proximal to the transducer is sampled near its origin from the internal carotid artery without the use of angle correction using a 1-2 mm sample volume (Mari et al., 2005). A peak systolic velocity (PSV) of 1.50 MoM in fetuses at risk of anaemia has a sensitivity for detecting anaemia of up to 100% (confidence interval 86-100%) in red cell alloimmunization as well as other cases of anaemia (Mari et al., 2000). In the context of diabetic pregnancies, maternal hyperglycemia is thought to cause an increase in fetal haematocrit, as cordocentesis has demonstrated a positive relationship between maternal hyperglycaemia and fetal polycythemia (Salvesen et al., 1992). Theoretically, the increase in blood viscosity due to polycythemia might be reflected by a corresponding decrease in blood flow velocity in the fetal circulation, which is opposite to the fetal anaemia model. This would be particularly prominent in affected macrosomic fetuses in gestational diabetes, who often suffer prolonged neonatal jaundice resulting from the polycythemia. However, such findings have not been consistently demonstrated in published reports.

In a prospective study of 138 singleton pregnancies with GDM, umbilical artery pulsatility index and middle cerebral artery pulsatility index were measured serially every 4 weeks from the diagnosis of GDM until delivery. A total of 305 Doppler examinations were performed with one to four examinations for each woman. About 27% (38) had one or more abnormal pregnancy outcomes: placental abruption, pre-eclampsia, preterm delivery, small-for-gestational-age, low Apgar scores, neonatal jaundice requiring treatment, sepsis, birth trauma, meconium aspiration syndrome, respiratory and neurological complications, However, there was extensive overlapping of the umbilical artery and MCA pulsatility indices, as well as MCA PSV values between those with normal and abnormal pregnancy outcomes. It was thus concluded that that Doppler studies of the umbilical and cerebral vessels were not useful for predicting outcome in these GDM pregnancies (Leung et al., 2004). In another cohort of 84 GDM pregnancies, it was found that stratifying the fetuses into appropriate, small- and large-for-gestational-age did not give any better correlation between the umbilical or middle cerebral impedance indices, but did apparently show that the bigger fetuses had lower MCA PSV and higher mean umbilical venous flow velocity than the smaller fetuses (To et al, 2009). It has been proposed that the pathophysiological basis of altered placental vascular flow patterns in diabetic pregnancies was functional, related to hyperglycemia induced thromboxane/ prostacyclin ratio imbalance (Saldeen et al., 2002), rather than to structural abnormalities related to trophoblastic invasion during development of the placental vascular bed. Thus, the abnormal umbilical waveforms and abnormal placental-cerebral Doppler ratios that were observable in non-diabetic pregnancies with fetal growth restriction would not be applicable to gestational diabetic pregnancies without significant growth restriction. The observation of lower MCA PSV in

the larger or macrosomic fetuses might be compatible with this hypothesis. In short, in the absence of pre-eclampsia or significant fetal growth abnormalities, the use MCA Doppler in diabetic pregnancies appears to have limited value.

3.4 Umbilical Vein waveform and umbilical venous flow volume

Arterial waveforms describe downstream resistance in critical vascular beds, in which disease or response to pathological conditions causes blood flow alterations. Venous Doppler, however, provides important cardiac data about stressed fetal circulations. Potential targets include the umbilical vein, inferior vena cava and the ductus venosus, while regional networks such as the hepatic, superior vena cava, intracranial and pulmonary veins have not provided clinically relevant cardiac indicators (Harman et al., 2003). By mid second trimester, the fetal umbilical vein normally has a continuous blood flow pattern, but this pattern can become pulsatile in pathological conditions, such as in significant fetal growth restriction and in hydropic fetuses. Thus, for umbilical venous waveforms, it has been advocated that a qualitative assessment of continuous versus pulsatile blood flow is used (Mari et al., 2008). Such venous pulsations most likely represent severe and critical fetal myocardial dysfunction and usually only appear at very late stages of fetal compromise. Umbilical venous waveforms are therefore not useful as an early sign for assessment of fetal well being for timing delivery.

The use of umbilical venous volume flow based on calculations of the cross-sectional area of the umbilical vein has been used and reported in previous studies to have a high degree of reproducibility (Boito et al., 2003). There have been suggestions for using the intra-abdominal portion of the umbilical vein (Haugen et al., 2004), as the latter would be less mobile than a free cord loop. Empirical experience showed that the demand on technical expertise between the two sites were largely similar, though the variations in the diameter of the intra-hepatic umbilical vein along its length could be somewhat higher than that of the free cord loop, and calculations of its cross-sectional diameter more complicated. In addition, since routine umbilical arterial Doppler would be performed on a free cord loop, it would be practical and convenient to extend the measurements to the adjacent vein within the cord segment (To & Mok, 2009).

To evaluate whether umbilical and middle cerebral arterial Doppler indices and umbilical venous volume flow are reflective of maternal gestational diabetic states, and whether such indices would be associated with the size of the fetus, a prospective observational study was performed in a cohort of 84 GDM pregnancies and compared with 62 non-diabetic controls. It was found that the mean pulsatility index values for the umbilical artery and the mean total umbilical venous flow (TUVF) and TUVF per unit birth weight did not differ significantly between diabetic and non-diabetic pregnancies. Large-for-gestational-age fetuses showed higher TUVF than normal size fetuses, but the TUVF per unit birth weight was higher for small-gestational-age fetuses. These differences were independent of their diabetic status. The only significant differences between non-diabetic and diabetic pregnancies in the data appeared to be the difference in the diameter and the mean flow volume of the umbilical vein, which were again probably more likely to be related to the size of the fetus. It was thus concluded that umbilical venous Doppler measurements near term were unable to distinguish between diabetic and non-diabetic pregnancies, and that umbilical venous flow volume was apparently more sensitive to the size of the fetus than to the maternal diabetic state (To & Mok, 2009). As fetal size variations could be secondary to

poor maternal glycemic control, and macrosomic fetuses would demonstrate such measurements, it might be argued that the total umbilical venous flow would still indirectly reflect fetal conditions, or the presence or absence of macrosomia. However, it is obvious that direct measurement of fetal growth parameters would be more precise in defining fetal overgrowth.

The mean total umbilical venous flow has been shown in previous studies to be related to the total cardiac output of the fetus, so that the larger fetus with a higher cardiac output would have higher flow volumes (Boito et al., 2003). It was not surprising that when controlled for birthweight, the mean total umbilical venous flow differences between large- and small-for-gestational-age fetuses were greatly attenuated. Recent data have shown that in growth restricted fetuses, there would be a preferential distribution of umbilical venous flow to the ductus venosus rather than via the fetal liver (Bellotti et al, 2004). However, whether such venous shunting mechanisms would be responsible for the observed higher mean umbilical venous flow per unit weight in small-for –gestational-age fetuses as compared to larger ones would require further evaluation. In diabetic pregnancies, on the other hand, it has been found that fetal liver volume could be associated with accelerated growth in these fetuses, though only marginal differences could be shown in the umbilical venous volume flow. Further studies to compare growth and TUVF volumes in fetuses within a large non-diabetic population would be of value to study the differences in circulatory volumes in relation to size of the fetus.

3.5 Artioventricular valves

The atrioventricular values (mitral and tricuspid) are characterized by two peaks – the "E" wave corresponding to the rapid filling of the ventricles and the "A" wave that corresponds to the atrial contraction. The "A" wave is taller than the "E" wave, and may reflect the stiffness of the fetal cardiac chambers. With advancing gestation, the E/A wave ratio increases. By contrast, after birth, the "E" wave will be taller than the "A" wave. In growth restricted fetuses, the two waves become abnormal (the E/A ratio increases) and in severe cases, there will be tricuspid and mitral regurgitation (Rizzo et al., 1988). Thus, in the study of diabetic pregnancies, such studies would be of value only if the pregnancy is complicated by severe fetal growth restriction.

3.6 Ductus venosus Doppler waveforms

The ductus venosus provides a unique combination of data, as it is the primary regulator of venous return in both normal and abnormal fetuses and is also a direct conduit of right atrial retrograde pulse waves (Harman et al., 2003). The ductus waveform is responsive to changes in oxygenation independent of cardiac function, and it is readily imaged because of its very high focal velocity on colour Doppler from early second trimester onwards. Ductus venosus waveforms are characterized by two peaks, the S and D, followed by a nadir, the atrial wave. Haemodynamically, these phases reflect the rapid chronologic change in pressure gradients between the umbilical vein and the right atrium. In normally grown fetuses, there is forward flow at the ductus venosus, and the pulsatility index for veins (S-D/a) decreases with advancing gestation. In growth restricted fetuses, the pulsatility index increases, and in the most severe cases, there will be reverse flow in the atrial wave.

Ductus venosus waveform deterioration precedes and predicts changes in biophysical profile score that indicate need for delivery (Baschat et al., 2003). This deterioration is

hypothesised to be the result of a volume/pressure effect, in which excess afterload is transmitted through the heart, and myocardial dysfunction appears as an end-stage compromise. A second indication of ductus venosus Doppler occurs at 12-14 weeks in conjunction with nuchal translucency screening and uterine artery screening. Abnormal retrograde atrial waves are a strong predictor of fetal cardiac abnormality, and also a good predictor of Down syndrome (Bilardo et al., 2001). Given the higher risks of congenital cardiac abnormalities in pregnancies complicated by pre-existing diabetes mellitus, ductus venosus screening at this gestation may have a role. There is as yet, scanty data in the literature that describe the use of ductus Doppler specific to diabetic pregnancies, and the application of ductus Doppler largely refers to that of growth restricted fetuses in general.

To evaluate the ability of the ductus venosus Doppler to predict adverse perinatal outcome in pregnancies complicated by pre-existing diabetes mellitus, a prospective study that included 82 women with pre-existing diabetes mellitus was performed. The ductus venosus Doppler index was defined as abnormal if the ductus venosus peak velocity index for veins was equal to or greater than the 95th percentile for gestation. Abnormal ductus venosus index was identified in 30.5% (n=25). Adverse perinatal outcome was identified in around one-third of these with abnormal indices (8/25) compared to 12.3% (5/57) with a normal ductus index. The sensitivity of the ductus venosus index in predicting adverse perinatal outcome in pre-existing diabetic pregnancies was thus 53.3% and specificity was 74.5%, with a positive predictive value of 32% and negative predictive value of 87.7%. The authors concluded that it should be useful to include ductus venosus Doppler indices as part of antenatal screening of pregnancies complicated by pre-existing diabetes mellitus (Wong et al., 2010).

4. Practical application of Doppler studies to diabetic pregnancies

It has thus been postulated that the degree of glycemic control would have more impact on the Doppler study results rather than directly related to the diabetic state (Bracero et al., 1991). The lack of association of Doppler parameters to maternal diabetic state was particularly true when the pregnancy was not complicated by fetal growth restriction or pre-eclampsia. While higher incidences of adverse outcome in diabetic pregnancies were related to the occurrence of such complications or to poor glycemic control with macrosomia, Doppler studies have apparently only limited effectiveness in predicting adverse perinatal outcome in these fetuses. Summing up the available data from the literature, a basic protocol for the sequential use of Doppler studies in both pre-existing and gestational diabetic pregnancies can be proposed (Table 1). Nevertheless, the clinical effectiveness of such a protocol still remains to be evaluated.

5. Summary

Available randomized control data and observational data have failed to demonstrate any consistent association between maternal diabetes and abnormal umbilical arterial Doppler indices. Doppler measurements of other fetal vessels apart from the umbilical arteries, such as the fetal descending aorta and the middle cerebral artery resistance indexes, or the peak systolic velocity of the middle cerebral arteries have also been studied in GDM pregnancies, and a similar lack of predictability for adverse outcome was generally found. The lack of

Gestation (weeks)	Vessel	Doppler parameters	Primary endpoint	PDM or GDM
12	DV	Retrograde atrial waves	aneuploidy; congenital cardiac abnormalities	P/GDM
	Uterine	Notching, PI	FGR	PGD
22-24	Uterine	Notching, PI	FGR	PGD
	UA, MCA	PI, CPR	FGR	PGD
3rd trimester	UA, MCA UV AV valves DV	PI, CRP, PSV PI, TUVF AV flow, TR, MR Retrograde atrial valves	FGR	PGD/ GDM

PDM: pre-existing diabetes mellitus, GDM: gestational diabetes mellitus, DV: ductus venosus
PI: pulsatility index, CRP: cerebral placental ratio, FGR: fetal growth restriction,
PSV: peak systolic velocity, AV: atrioventricular, TR: tricuspid regurgitation, MR: mitral regurgitation

Table 1. Sequential Doppler applications foe diabetic pregnancies

association of Doppler parameters to maternal diabetic state was particularly true when the pregnancy was not complicated by fetal growth restriction or pre-eclampsia. While higher incidences of adverse outcome in diabetic pregnancies were related to the occurrence of poor glycemic control with macrosomia and polyhydramnios, conventional arterial Doppler indexes and cerebral /placental Doppler ratios have not been shown to be effective in picking up these high risk fetuses. The use of umbilical venous Doppler and venous volume flow based on calculations of the cross-sectional area of the umbilical vein has been reported in various studies to have a high degree of reproducibility. Venous volume flow measurements have not been found to be consistently reflective of maternal gestational diabetic states. Such volume flow measurements apparently reflected well the fetal growth and size and thus indirectly the glycemic control and the risks of perinatal complications. Doppler studies of other venous sites, including the intraabdominal/ intrahepatic portion of the umbilical vein, or the ductus venosus have also been studied with variable results. Whether such measurements could be used directly for monitoring fetal well being requires further evaluation.

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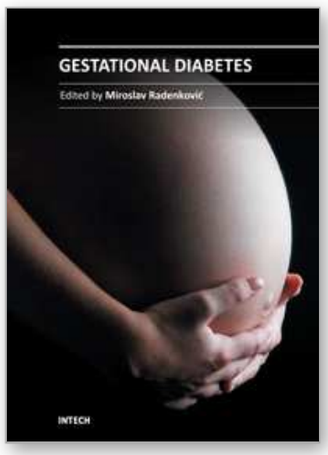

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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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