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CLINICAL ARTICLE

Correlation of maternal body mass index with umbilical artery Doppler in pregnancies complicated by fetal growth restriction and associated outcomes

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Synopsis

Maternal BMI correlates with abnormal umbilical artery Doppler findings and outcomes in growth restricted babies but does not affect feasibility of Umbilical artery Doppler.

Abstract

Objective: To evaluate the correlation between Umbilical Artery (UA) Doppler and its feasibility across categories of maternal BMI in the presence of foetal growth restriction (FGR).

Methods: 1074 Singleton pregnancies with suspected FGR on ultrasound examination between 24+0 and 36+0 weeks' gestation were reviewed. Evaluation of the UA Doppler was performed at 1-2 weekly intervals. Abnormal UA Doppler findings and delivery outcomes were compared between the different maternal BMI categories.

Results: Increased UA pulsatility index (PI > 95th centile) was reported in 81% of obese category 2 patients (BMI <35 - 39.9 kg/m2) compared to a 46% incidence in the remaining categories, normal (BMI <24.9 kg/m2), overweight (BMI <25 - 29.9 kg/) and obese class 1 (BMI <35 - 39.9 kg/m2) (p = 0.001). In absent or reversed end diastolic flow (AEDF/REDF) we found an increasing incidence across the BMI categories (4%-25%) (p<0.0001). Higher maternal BMI was associated with Lower birthweights and higher C-section rates. Increasing maternal BMI did not affect successful assessment of UA Doppler.

Conclusion: There is a positive correlation between increasing maternal BMI and abnormal UA Doppler findings in FGR. Maternal BMI may be considered as an additional risk factor when evaluating UA Doppler for placental insufficiency.

1 Introduction

Maternal obesity is a growing epidemic in the developed world [1]. Well recognized associated pregnancy complications include pre-eclampsia, gestational diabetes and increased rates of infection and caesarean delivery [2, 3, 4, 5, 6, 7]. It has been proposed that some adverse pregnancy outcomes in obese patients may be mediated by placental insufficiency. Given that utero-placental insufficiency is typically associated with foetal growth restriction (FGR), the presence of increasing maternal body mass index (BMI) in the setting of FGR may further compound the risk of adverse outcome [8].

Sonographic assessment of UA Doppler is widely accepted as a useful tool in the surveillance of pregnancies complicated by FGR [9, 10 11, 12]. Doppler ultrasound study of UA waveforms can identify the compromised fetus and assist in timing of delivery. However, successfully assessing the UA Doppler may be challenging in the presence of significant maternal obesity. The objective of this secondary analysis of the Prospective Observational Trial to Optimize Pediatric Health (PORTO) in FGR was to establish the relationship between maternal BMI and abnormal UA Doppler changes. Our aim was to assess whether there was a correlation between abnormal UA findings in FGR fetuses and increasing maternal BMI and evaluate the outcomes. We also questioned feasibility (obtainability) of UA Doppler across the categories of BMI. Our hypothesis is that increasing maternal BMI negatively impacts on placental perfusion which is reflected in Doppler velocimetry findings and delivery outcomes.

2 Materials and Methods

Between January 2010 and June 2012, the PORTO Study recruited 1,200 consecutive ultrasound-dated singleton pregnancies at seven academic obstetric centres in Ireland. Inclusion criteria were a gestational age between 24^{+0} and 36^{+6} weeks' gestation and an EFW < 10^{th} centile confirmed by a research sonographer on ultrasound. Only fetuses ≥ 500 grams were eligible to be recruited to the study. FGR was defined as EFW <the 10^{th}centile based on sonographic measurements of foetal biparietal diameter, head circumference, abdominal circumference and femur length (Hadlock-4). Fetuses with major structural and/ or chromosomal abnormalities were excluded retrospectively from the final analysis. All study participants gave written informed consent which was approved by the institutional review board and in accordance with the guidelines from the declaration of Helsinki.

Umbilical artery Doppler assessment was performed at enrolment (between 24-36 weeks' gestation) and every 1-2 weeks until delivery. EFW was assessed every 2 weeks along with amniotic fluid index and biophysical profile. All Doppler assessments were performed by a small group of trained research sonographers. While the study was multicentre in nature, consistency in standards of ultrasound assessment were assured by pre study training and ongoing regular training sessions for the cohort of research sonographers by experienced maternal foetal medicine specialists. All sonographers used the same

ultrasound equipment (Voluson ® E8, GE Healthcare) and underwent regular quality assurance assessments. The UA PI was obtained by using colour Doppler in free loops of the umbilical cord, keeping the angle of insonation with the examined vessel as close to zero as possible and was calculated using the automatic trace and recorded. Abnormal UA Doppler was defined absent or reversed end diastolic flow or a UA-PI >90th centile. Obtainability of UA PI (yes/no) was recorded on ultrasound examination.

Baseline demographic data were recorded on all participants including maternal BMI at the prenatal booking visit (11-14 weeks' gestation). Maternal BMI was divided into 4 subcategories: normal (BMI <24.9 kg/m^2), overweight (BMI <25 - 29.9 kg/m^2), obese class 1 (BMI <30 - 34.9 kg/m^2) and obese class 2 (BMI <35 - 39.9 kg/m^2). There were no patients in obese class 3 (BMI >40). All prenatal and ultrasound data were contemporaneously transferred to an ultrasound software system (Viewpoint®; MDI viewpoint, Jacksonville, FL) and uploaded onto a live web-based central consolidated database. The delivery data and neonatal outcomes were recorded from patient's charts and transferred to the database for analysis. Composite perinatal morbidities were recorded (Table 4).

Comparisons across all BMI groups were performed using the Cochrane-Armitage trend test and ANOVA analysis (Tables 1 & 4), dependent upon variable type analyzed. Pairwise BMI group comparisons of AEDF/REDF and Abnormal UA (inclusive of AEF/REDF) were obtained from a logistic regression analysis (Table 2). In addition, a multiple logistic regression was performed including the following covariates: age, smoking status, ethnicity and PIH/PET status. Comparisons of UA PI obtainability over the course of a pregnancy between BMI group pairs were performed using the Wilcoxon Rank-sum test (Table 3). Given our study design, an inter-rater reliability analysis of obtainability was not possible. Statistical significance was considered at the 5% nominal level. All data management and statistical analyses were performed using SAS 9.4.

3 Results

1116 out of the 1,200 recruited pregnancies with EFW <10th centile completed the study protocol in the primary PORTO study. A further 40 patients did not have their BMI recorded at the time of recruitment. Of the 1,074 recruited patients with complete records

for this secondary retrospective analysis 691 (64%) were of normal weight (BMI<25), 258 (24%) were overweight (BMI 25-30), 93 (9%) were obese class I (BMI 30-35) and 32 (3%) were obese class II (BMI 35-40). There were no patients enrolled in the study in obese class 3 (BMI >40). The majority of our patients were white European ethnicity (82%) with an average age of 30 years, 24% of patients were smokers. Maternal demographics and fetal characteristics representing the study group according to BMI category can be seen in table 1. There was an increase in PIH/PET seen as maternal BMI increases, 9% of normal BMI and 50% of obese class 2 patients.

We found an increasing incidence of AEDF/REDF with increasing category of BMI (4% of normal BMI patients; 10% of overweight patients; 11% of obese class 1 patients, and 25% of obese class 2 patients (p-value 0.0001)(table 2). In abnormal UA Doppler findings defined as raised UA Doppler pulsatility index (AEDF/REDF or PI > 95thcentile) there was not a clear trend. Across the categories of normal BMI, overweight and obese class 1, 45-46% were reported as abnormal Doppler findings however this increased in obese class 2 patients to 81% (p-value = 0.001) with statistical significance remaining after adjustment for covariates.
Obese class II patients were delivered earlier at an average gestational age of 35.5 weeks' compared to patients with normal BMI at 38.1 weeks' gestation. As a consequence, mean birth weight was negatively correlated with maternal BMI. Lower spontaneous vaginal deliveries and higher elective caesarean section rates were also seen with increasing maternal BMI (table 4). Overall we found a significant increase in the composite perinatal morbidity (p<0.0001) in obese class 2 patients (Table 4)
UA Doppler velocimetries were successfully obtained across all BMI categories in 88-92% of patients with an average number of 6/7 scans per patient. (Table 3).

4 Discussion

Up to 10% of all pregnancies are affected by FGR and are therefore at increased risk of adverse outcomes including neonatal morbidity and mortality [8]. The global relevance of abnormal UA Doppler findings (increased UAPI), AEDF and REDF on ultrasound examination associated with FGR suggests that the fetus is becoming increasingly stressed and at risk of hypoxia and acidosis. Adverse outcomes are predominantly

associated with abnormal UA Doppler and are uncommon in FGR where the blood flow is normal [17]. While poor placental perfusion is usually associated with early onset FGR due to abnormal villious branching development in designated placentas and indeed many of our patients delivered early, abnormal UA Doppler findings also presented later in the third trimester suggesting placental insufficiency. Furthermore, recent placental studies have supported the notion of an association between obesity and placental dysfunction, where higher levels of vascular lesions were found in the examined placentas of obese women compared with normal weight women [18]. Another study examining placentas of obese women showed lower levels of the taurine transporter protein (Tau T) in obese women compared to women of normal weight. Tau T is a β amino acid with antioxidant properties and is required in foetal growth and organ development, and lower levels of this protein suggests compromised placental development and function [19].

While maternal obesity is usually associated with large-for-gestational age fetuses, [20] a study by Sarno et al.[3] found no significant birth weight difference across the categories of BMI in uncomplicated pregnancies. They suggest that perhaps some fetuses are failing to reach their potential in-utero growth trajectory despite falling within the normal birth weight range. In the same study, increased UAPI was found to be positively correlated with maternal BMI in a single third trimester scan, further suggesting placental insufficiency as maternal BMI increases [3]. More recently Tuelings et al have demonstrated that blood flow is impaired in the uterine and umbilical artery in patients with high maternal BMI [21]. Our study results agree with these findings also demonstrating a positive correlation between increased UA-PI and maternal BMI with delivery at earlier gestations and lower birth weights. This supports the theory that increasing maternal BMI may preclude a fetus reaching its growth potential and increases the risk of overall adverse outcome. A strength of our study is that the UA Doppler was assessed at least every 2 weeks, and sometimes more frequently depending on the severity of FGR. Patients across the categories of maternal BMIs had an average of 6/7 scans (table 3). Our findings are therefore based on a range of values per patient and at frequent stages in the third trimester up until delivery where close monitoring was necessary. The care/delivery plan was at the discretion of the managing clinical team.

Some studies argue that the sensitivity of obtaining accurate ultrasonographic information is limited in overweight and obese patients [13, 14].

Contemporary opinion would cite the limitations of early-pregnancy and anomaly ultrasonograms in the setting of increasing BMI. This was not found to be the case for this study, with respect to third trimester assessment of fetal growth and UA Doppler studies. In this study 88-92% of UA Doppler values were obtained, demonstrating that Doppler studies on umbilical arteries are achievable in the third trimester across all categories of maternal BMI. This coincides with accuracy of ultrasound EFW in this group as our results show that EFW was within 6.6% of the actual birth weight across all categories of BMI [15].

In recent years manufacturers of ultrasound equipment have improved imaging techniques to counteract the negative effect of maternal obesity on obtaining good quality images. By reducing the mean array emission frequency, this has allowed users to gain better images at deeper penetration levels. This helps in obtaining better images in larger patients, where the fetus is further away from the ultrasound probe. All possible pre- and post-processing filters and techniques are used to increase the signal-to-background noise ratio. Tissue harmonic imaging has been shown to improve image quality in obese individuals [14, 16].

For validation of our findings and accuracy of our results a small number of highly trained sonographers performed the UA Doppler ultrasound for this study. However, UA Doppler is now routinely used in clinical practice and therefore these results should be achievable outside the remit of a research study within the standard care delivered to obstetric patients.

A limitation of this study is that maternal BMI was recorded once, at the booking visit (12-14 weeks' gestation), and therefore maternal weight gain or weight loss near-term was not recorded. However this was a high risk group, with variations in gestational age at delivery ranging from 24-40 weeks' due to FGR, and sometimes in emergency settings, and therefore it was not achievable to weigh patients pre delivery. The impact of maternal weight gain or loss may have contributed to the perinatal outcomes and therefore cannot be concluded in this study. Another limitation is that pre pregnancy smoking and number of cigarettes were not recorded only that the mother smoked during this pregnancy. Other

confounding factors such as maternal age, race, history of preeclampsia and hypertension were examined according to BMI category and preeclampsia/hypertension was the only other demographic that increased according to BMI category in our study patients. (Table 1). In the evaluation of obtainability, our study design did not permit an inter-rater reliability analysis.

While many studies have recommended education on diet and exercise, and provided counselling regarding maintaining a healthy lifestyle pre and during pregnancy, such interventions have yet to translate into the successful prevention of obesity-related complications [4, 22].

5 Conclusion

Pulsatility index in the UA Doppler is a key predictor of adverse pregnancy outomes in FGR and reflects resistance in feto placental circulation. While other maternal comorbidities influence placental insufficiency in early and late onset FGR the presence of maternal obesity may be considered as an additional risk factor. A correlation exists between increasing maternal BMI (25-40), abnormal UA Doppler velocimetries and poorer delivery outcomes in FGR with further research needed. The UA Doppler is easily obtained in the third trimester across all categories of maternal BMI.

AUTHOR CONTRIBUTIONS

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DISCLOSURE OF INTERESTS

None of the authors have a conflict of interest.

DETAILS OF ETHICS APPROVAL

Ethics approval was obtained from the Rotunda Hospital
Research Ethics Committee before commencing this study in 2009.
and the study complied with the Declaration of Helsinki.

Full written consent was obtained from all participants
before inclusion in this study.

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TABLE 1. Maternal demographics (N=1074)

Characteristic	BMI Group				P-value
	Normal (N=691)	**Overweight** (N=258)	**Obese Class I** (N=93)	**Obese Class II** (N=32)	
Age (years)	29 ± 6	32 ± 6	30 ± 6	32 ± 6	<0.001
Age > 30 years	120 (17%)	76 (29%)	13 (14%)	9 (28%)	0.058
White European Ethnicity	567 (82%)	201 (78%)	74 (80%)	29 (91%)	0.194
Spontaneous Conception	683 (99%)	252 (98%)	92 (99%)	31 (97%)	0.960
Smokers	181 (26%)	57 (22%)	17 (18%)	4 (13%)	0.098
PIH/PET	62 (9%)	41 (16%)	22 (24%)	16 (50%)	<0.001
GA at enrolment (weeks)	30 ± 4	29 ± 4	30 ± 4	28 ± 3	0.015

Note: Categorical data are presented at n (%), continuous data are presented as mean ± SD. P-values are from the Cochrane-Armitage trend test or ANOVA.

TABLE 2. Absent end diastolic flow/reversed end diastolic flow (AEDF/REDF and Abnormal Umbilical artery Doppler (Increased Pulsatility Index) according to maternal body mass index

BMI Group	**AEDF/REDF**			
	No 1001 (93%)	**Yes** 73 (7%)	**OR (95% CI)**	**P-value**
Normal	661 (96%)	30 (4%)	-	-
Overweight	233 (90%)	25 (10%)	2.36 (1.36 – 4.10)	0.002#
Obese Class I	83 (89%)	10 (11%)	1.63 (1.12 – 2.37)	0.011
Obese Class II	24 (75%)	8 (25%)	1.94 (1.45 – 2.61)	<0.001#
	Abnormal UA			
	No 579 (54%)	**Yes** 495 (46%)	**OR (95% CI)**	**P-value**
Normal	382 (55%)	309 (45%)	-	-
Overweight	140 (54%)	118 (46%)	1.04 (0.78 – 1.39)	0.779
Obese Class I	51 (55%)	42 (45%)	1.01 (0.81 – 1.25)	0.936
Obese Class II	6 (19%)	26 (81%)	1.75 (1.30 – 2.36)	<0.001#

Notes: Percents are row-percents. Odds-ratio (OR), 95% confidence interval (CI) and p-value from a logistic regression with the Normal BMI group as comparator.
statistically significant after adjustment for age, smoking status, ethnicity and PIH/PET status.

TABLE 3. Obtainable UA Doppler (%) according to BMI Group (N=1074)

BMI Group	N	Ultrasound assessments per patient Median	Obtainable UA# Median % (95% CI)	P-value
Normal (BMI<25)	691	6	89% (88% - 90%)	-
Overweight (BMI 25-30)	258	7	90% (87%- 93%)	0.378
Obese Class I (BMI 30-35)	93	6.5	86% (81% - 91%)	0.566
Obese Class II (BMI 35-40)	32	7	90% (88% - 92%)	0.318

Obtainable UA is percent per patient.
Wilcoxon Rank-sum test with the Normal BMI group as comparator.

TABLE 4. Delivery and Neonatal Outcomes according to BMI category (N=1074)

Characteristic	BMI Group				P-value
	Normal (N=691)	**Overweight** (N=258)	**Obese Class I** (N=93)	**Obese Class II** (N=32)	
GA at delivery (weeks)	38.1 ± 2.6	37.5 ± 3.3	37.2 ± 3.5	35.5 ± 4.3	<0.001
Birth weight (kg)	2.5 ± 0.6	2.5 ± 0.7	2.4 ± 0.8	2.0 ± 0.9	<0.001
Spontaneous Vaginal delivery	377 (55%)	122 (47%)	36 (39%)	8 (25%)	<0.001
Elective Cesarean section	106 (15%)	50 (19%)	24 (26%)	13 (41%)	<0.001
Emergency Cesarean section	130 (19%)	66 (26%)	26 (28%)	9 (28%)	0.006
Instrumental vaginal delivery	78 (11%)	21 (8%)	7 (8%)	2 (6%)	0.082
NICU admission	173 (25%)	78 (30%)	36 (39%)	15 (47%)	0.001
Composite perinatal Morbidity	19 (3%)	20 (8%)	8 (9%)	7 (22%)	< 0.001
Perinatal Mortality	3 (< 1%)	0	2 (2%)	1 (3%)	0.036

Notes:

(1) Categorical data are presented at n (%), continuous data are presented as mean ± SD

(2) P-value from the Cochrane-Armitage trend test or ANOVA.

(3) *Composite perinatal morbidity includes intraventricular haemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death.