DE-NOVO ABNORMAL UTEROPLACENTAL CIRCULATION IN THE THIRD TRIMESTER: PREGNANCY OUTCOME AND PATHOLOGICAL IMPLICATIONS

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Short Title: Uterine artery Doppler worsening and pregnancy hypertension

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ABSTRACT

Objective: Hypertensive disorders of pregnancy (HDP) are associated with impaired placentation, as evidenced by abnormal uterine artery (UtA) Doppler. UtA mean pulsatility index (PI) shows a progressive decline with gestational age (GA). However, previous studies have reported that a proportion of pregnancies demonstrate worsening of the UtA Doppler. The aim of this study was to investigate

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the incidence of HDP according to the change in the UtA mean PI between the second and third trimester.

Methods: This cohort study included singleton pregnancies undergoing longitudinal UtA Doppler assessment in the second and third trimester. All the parameters were converted into centiles and multiples of the median (MoM) adjusting for GA. The study cohort was divided into 2 groups according to the change in the UtA Doppler between the second and third trimesters (decline or no change vs increase in the mean PI MoM). HDP included women who developed pre-eclampsia and gestational hypertension. Regression analysis was used to adjust for potential confounders.

Results: The analysis included 5887 pregnancies. The incidence of HDP was significantly higher in the group with worsening of the UtA mean PI compared to those without (7.9% vs 5.8%; $p<0.002$). Logistic regression analysis demonstrated that both the second trimester UtA PI MoM (OR 8.12, 95% CI 5.07-13.00; $p<0.001$) and the difference between the 2 trimesters (OR 3.41, 95% CI 2.434-4.768; $p<0.001$) were significant independent predictors for the development of HDP.

Conclusion: Worsening of the UtA Doppler, independent of the value recorded in the second trimester, is associated with HDP.

INTRODUCTION

Over the last three decades, assessment of the uteroplacental circulation has been commonly conducted by examining the Doppler velocimetry of the uterine arteries[1]. Impaired placentation, secondary to inadequate trophoblastic invasion of the spiral arteries, is thought to result in increased impedance to the flow within the uterine arteries[2-5]. The clinical consequences of impaired placentation include pre-eclampsia[6,7],fetal growth restriction[8], placental abruption[9] and stillbirth[10] – collectively known as 'placental syndromes'. Several studies have reported raised uterine artery pulsatility index (UtA PI) in the first and second, and more recently in the third, trimesters in the pregnancies subsequently complicated by preeclampsia[11,12]. Despite the fact that the predictive value of the UtA PI is lower for the late-onset compared to the early-onset preeclampsia, recent data on third trimester UtA PI assessment has shown improved screening efficiency for late-onset preeclampsia[11,12,13,14].

The UtA PI decreases with gestational age, presumably as trophoblastic invasion continues and is completed[15]. In the majority of the pregnancies presenting with abnormally raised UtA PI in the first trimester, the indices normalise with advanced gestation[16]. However, in those pregnancies destined to develop adverse pregnancy outcome, in particular preeclampsia, the previously recorded elevated UtA PI persists[12]. Increased UtA PI values in the third trimester are also associated with adverse perinatal outcomes such as stillbirth and perinatal death[17-21]. Interestingly, a few studies have reported apparently de-novo abnormal third trimester UtA PI in a proportion of pregnancies where normal UtA PI values were recorded earlier in pregnancy[22]. Some of these patients developed preeclampsia and fetal growth restriction (FGR), suggesting an association with late-onset placental dysfunction. The aim of this study was to investigate the pattern of change in UtA PI with advancing gestation and the relationship to the development of preeclampsia.

METHODS

This was a retrospective cohort study conducted at a tertiary Fetal Medicine Unit between March 1997 and March 2016. All eligible pregnancies were identified by an electronic database search (Viewpoint 5.6.8.428, Wessling, Germany). The inclusion criteria were singleton pregnancies undergoing both second (18-23 weeks) and third (>26 weeks) trimester fetal and uterine artery Doppler ultrasound assessment during the defined study period. The study population consisted of both low and high-risk pregnancies, requiring a third trimester ultrasound scan primarily for fetal growth assessment. The indications for third trimester ultrasound scan included follow up for high second trimester UtA Doppler PI, reduced fetal movements, post dates evaluation, maternal medical disorders, previous history of FGR, fetal presentation and placental localization. Fetal abnormalities, aneuploidies, genetic syndromes, multiple pregnancies and pregnancies, which were lost to follow-up were excluded from the analysis.

All pregnancies were dated according to the crown-rump length (CRL) measurement in the first trimester[23]. When the first ultrasound measurement was performed after 14 weeks' gestation, the pregnancy was dated according to the head circumference in keeping with NICE guidelines. All the fetal ultrasound and Doppler assessments were performed by highly experienced operators. Routine fetal biometry was assessed and the estimated fetal weight (EFW) was calculated from the biparietal diameter, abdominal circumference and femur length using a formula by Hadlock *et al*[24]. Doppler parameters were recorded automatically from consecutive waveforms and measured during periods of fetal quiescence. An angle of insonation below 30° was employed. The umbilical artery (UA) waveform was recorded by assessing a single free loop of umbilical cord using the colour Doppler. The UA PI was calculated by applying a standard formula[25]. The middle cerebral artery (MCA) Doppler was recorded according to a standard protocol by obtaining a transverse section of the fetal head and identifying the vessel close to the circle of Willis using colour Doppler[26]. The cerebroplacental ratio (CPR) was determined as a ratio between the MCA PI and the UA PI[27]. The left and right uterine arteries were identified at the level of the crossover with the external iliac artery using colour Doppler. Pulsed wave Doppler was employed to measure the PI over three consecutive waveforms[28]. The

mean UtA PI of the left and right vessels was subsequently calculated and used for analysis. The UA PI, MCA PI and UtA PI were adjusted for gestational age and converted into multiples of the median (MoM)[28,29]. The difference between the third and second trimester UtA PI MoM was calculated by subtracting the values of the second trimester from the third trimester UtA PI MoM. An increase in value was considered from +0.01 PI MoM and a decrease from -0.01 PI MoM difference onwards. Estimated fetal weight and birth weight (BW) were adjusted for gestational age and converted into centiles[30].

Data on the maternal characteristics and pregnancy outcomes were collected from the hospital obstetric and neonatal records. The maternal characteristics investigated in this study included maternal age, body mass index (BMI), ethnicity (Caucasian, Asian, Black, Mixed, Others), parity (parous/nulliparous if no previous pregnancies beyond 24 weeks' gestation) and smoking. The study outcomes included the pregnancy outcome (live birth, stillbirth and neonatal death less than or greater than one week following delivery), incidence of hypertensive disorders in pregnancy (HDP), gestational age at delivery and BW. HDP were defined according to the criteria established by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[31]. Small for gestational age (SGA) was defined as BW below the 10th centile after correcting for gestational age at delivery. Stillbirth was defined as fetal demise after 24 completed weeks of pregnancy. Although data integrity was aimed to be as high as possible, less than 10 percent missing data was achievable for all parameters.

Statistical analysis

Data distribution was assessed by the Kolmogorov- Smirnov test of normality. All data were expressed as median and interquartile range (IQR). The Mann-Whitney U test was used to compare continuous variables that were not normally distributed. Categorical variables were compared using the Chi-Square test and values were described as numbers (%). Logistic regression analysis was used to assess the association of HDP with maternal characteristics, second (or third) trimester UtA PI MoM and the difference between the third and second trimester UtA PI MoM. A p value <0.05 was considered statistically significant. Statistical software (SPSS 24.0; SPSS Inc, Chicago, IL) was used to conduct the analysis.

RESULTS

During the study period, 6044 women underwent fetal ultrasound and Doppler assessment in the second and third trimester. We excluded 157 pregnancies due to the diagnosis of fetal aneuploidy, structural anomaly or missing follow-up data. The remaining 5887 singleton pregnancies, containing 1070 (17.7%) high-risk pregnancies, were included in the analysis. The median gestational ages at second trimester and third trimester UtA Doppler were 21.7 (IQR 21.43- 21.86) and 36.3 (IQR 35.86- 38.43) weeks, respectively. The prevalence of SGA birth and HDP in the cohort was 16.2% and 6.6%, respectively.

The cohort was divided according to patients who demonstrated an increase in UtA PI (n=2177) and those where there was a decrease or stable UtA PI (n=3710) between the second and third trimesters (Table 1). Women who demonstrated a de-novo rise in third trimester UtA PI were more likely to have an SGA baby ($p<0.001$), to develop HDP ($p=0.002$) and to deliver at an earlier gestation ($p<0.001$). They also had significantly higher UA PI ($p<0.001$), lower MCA PI ($p<0.001$) and lower CPR ($p<0.001$).

Women with HDP were significantly older ($p=0.035$), had a higher BMI ($p<0.001$) and were more likely to have Afro-Caribbean ethnic origin ($p<0.001$) compared to those without HDP (Table 2). Both second and third trimester UtA PI MoMs were significantly ($p<0.001$) higher in women with HDP when compared to the non-HDP cohort. Logistic regression analysis to assess the relationship between maternal age, BMI, ethnicity, second and third trimester UtA PI MoM was conducted in women with HDP. All parameters, excluding maternal age, were significantly associated with development of HDP (Table 3).

DISCUSSION

A proportion of pregnancies demonstrate de-novo increase in third trimester UtA PI, and the latter finding is associated with a higher prevalence of HDP, SGA birth as well as fetal Doppler indices of hypoxemia. Development of HDP was independently associated with BMI, black ethnicity, raised UtA PI in the second trimester and de-novo third trimester increase in UtA PI.

Pathophysiological implications of study findings

Previous studies have demonstrated a progressive decrease in uterine artery resistance with advancing gestation to reach a nadir around 26-28 weeks' gestation and remaining at this level until term[12,15,32]. This pattern of change in uterine artery resistance is thought to reflect progressive trophoblast invasion of the myometrium and spiral artery conversion with advancing gestation – as evidenced by the relationship between first trimester UtA PI and trophoblast apoptosis, motility and invasion[2-5]. With this understanding of the relationship between trophoblast development and its effect on uterine blood flow, the findings of the current study are hard to reconcile. The demonstration of de-novo increase in third trimester UtA PI is unlikely to be related to changes in trophoblast invasion, as this would require hypothetical 'de-conversion' of the spiral arteries - a biological phenomenon not considered likely.

An alternative explanation is that the increase in third trimester UtA PI may be unrelated to changes in trophoblast. Previous reports of abdominal implantation of the placenta have shown a normal pattern of uterine artery blood flow changes as for normally implanted pregnancies[33-35]. A more plausible explanation for the late pregnancy uterine artery Doppler changes seen in the current study and abdominal pregnancy may lie with well characterized pregnancy changes in cardiac output, physical properties of blood and systemic vascular resistance[36]. The hypothesis that late pregnancy changes in UtA PI are caused by maternal hemodynamic changes and related to the subsequent development of HDP are supported by the finding that preeclampsia is associated with heart remodelling and significant impairment of cardiac function[37-40]. The latter hypothesis is consistent with emerging evidence that

the maternal cardiovascular profile may play an important role in determining whether women will develop preeclampsia[37,41-43].

If late pregnancy changes in uterine artery resistance are dependent predominantly on maternal hemodynamic alterations, then consideration has to be given to whether the previously observed high resistance first trimester uterine artery Doppler indices are an effect of or, in fact, cause poor trophoblast development. There are now a number of longitudinal studies of maternal hemodynamic changes that demonstrate very early pregnancy alterations in cardiac output and systemic vascular resistance that cannot be explained by variations in trophoblast development. The strong association between early pregnancy uterine artery resistance and subsequent development of HDP may then be explained more so by compromised maternal cardiac adaptation to pregnancy than impaired trophoblast development.

Although there is strong evidence that late onset increase in UtA Doppler PI is connected with impaired maternal hemodynamics as described above, there are studies on late-onset SGA fetuses that identified placental underperfusion in 66.7% of their placentae.[44] One-quarter of these lesions, representing placental underperfuaion, were due to distal villous hypoplasia[45] and about one half due to vascular obstruction[45] potentially also leading to an increase in uterine artery Doppler PI in the third trimester. The underlying mechanisms leading to these placental changes have not been fully identified yet and range from abnormal placentation to impaired maternal hemodynamics.

Clinical and research implications of study findings

The study findings show that the development of HDP and SGA birth in the third trimester is principally related to high mid-gestational UtA PI as well as de-novo increase in third trimester UtA PI. These findings are supported by previous work in a much smaller cohort of patients reporting abnormal third trimester UtA PI relative to first trimester values were associated with preeclampsia and FGR due to late onset placental insufficiency, independently of the impaired trophoblast invasion in the first trimester. The effect of longitudinal changes in UtA Doppler indices in pregnancy on the risk of developing preeclampsia were also investigated by Khalil *et al.* in a larger cohort of patients[15]. The authors demonstrated a significant increase in UtA PI in late

pregnancy in patients presenting with term PE. Interestingly and in concordance with our study, this increase was only apparent in the third trimester and not before[15].

In clinical screening terms, our study findings suggest that late pregnancy assessment of UtA PI – or maternal haemodynamic function – may improve both screening and detection of preeclampsia. Women who develop term preeclampsia have significantly diminished myocardial relaxation resulting in reduced myocardial performance and cardiac function[46]. These observations are supported by the epidemiological evidence of long-term cardiovascular morbidity in women who develop preeclampsia. The observation of late pregnancy increase in UtA PI may therefore be related to maternal cardiovascular dysfunction as it is a proxy marker for the development of preeclampsia. Increased UtA PI may also be a marker for postpartum cardiac dysfunction and strategies to reduce maternal cardiovascular risk should be developed.

Strengths and weaknesses

The strengths of our study include the large number of pregnancies included in the analysis, where confounding variables, such as gestational age, were adjusted for to ensure accurate interpretation of the data. Furthermore, regression analysis was conducted to examine the individual contributions of each parameter to the development of HDP. The main limitation of this study is its retrospective study design, and therefore, its inherent risk of selection bias – this may well be reflected in the small number of perinatal deaths in our cohort.

Conclusions

The study findings suggest that de-novo increase in the UtA PI in the third trimester of pregnancy predisposes to the development of HDP. This observed sudden worsening of the UtA Doppler in late pregnancy is unlikely to be related to impaired trophoblast development or reversal of spiral artery conversion, and suggests an alternative pathophysiological mechanism to placental insufficiency. Consideration should be given to other potential influences on the UtA Doppler indices and impaired trophoblast function, such as maternal cardiac dysfunction. The relationship between the maternal systemic circulation, in particular the cardiac function, and the uteroplacental circulation should be investigated in future studies.

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Conflict of Interest

All the authors declare that they have no conflict of interest.

Table 1. Comparison of the maternal and pregnancy characteristics according to the difference between the second and third trimester uterine artery (UtA) pulsatility index (PI) multiple of Medians (MoMs)

	Decreased/stable UtA PI MoM (n=3710)	**Increased UtA PI MoM (n= 2177)**	**P value**
Maternal age in years, median (IQR)	31.0 (27.0-35.0)	31.0 (27.0-35.0)	0.707
Body mass index in kg/m^2, median (IQR)	23.90 (21.40-27.60)	24.20 (21.63-28.80)	<0.001
Ethnicity			<0.001
Caucasian, n (%)	2285 (62.2)	1207 (55.9)	
Africo-Caribbean, n (%)	482 (13.1)	352 (16.3)	
Asian, n (%)	775 (21.1)	512 (23.7)	
Mixed, n (%)	112 (3)	79 (3.7)	
Others, n (%)	20 (0.5)	10 (0.5)	
Nulliparous, n (%)	2364 (69.8)	1284 (64.5)	<0.001
Smoking, n (%)	210 (5.9)	136 (6.6)	0.300
Birthweight centile, median (IQR)	40.60 (19.25- 66.09)	31.60 (12.19- 57.67)	<0.001
Pregnancy outcome			0.090
Livebirth, n (%)	3360 (99.9)	1940 (99.6)	
Stillbirth, n (%)	3 (0.1)	7(0.4)	
Neonatal death<1 week, n (%)	2 (0.1)	1(0.1)	
Hypertensive disorders in pregnancy, n (%)	215 (5.8)	171 (7.9)	0.002
Small for gestational age, n (%)	434 (13.1)	416 (21.4)	<0.001
Third trimester umbilical artery PI MoM, median (IQR)	1.07 (0.96-1.19)	1.10 (0.98-1.22)	<0.001
Third trimester middle cerebral artery PI MoM, median (IQR)	0.95 (0.85- 1.07)	0.93 (0.84- 1.06)	<0.001
Third trimester cerebroplacental ratio (CPR) MoM, median (IQR)	0.99 (0.86- 1.15)	0.96 (0.82- 1.11)	<0.001
Low CPR, n (%)	151 (4.2)	159 (7.6)	<0.001
Gestational age at delivery in weeks, median (IQR)	40.14 (39.0- 41.14)	39.71 (38.57- 40.86)	<0.001

IQR: interquartile range

Table 2. Comparison between the pregnancies complicated by hypertensive disorders in pregnancy and normotensive pregnancies

	Pregnancies with Hypertensive disorders in pregnancy (n= 386)	**Normotensive pregnancies (n=5501)**	**P value**
Maternal age in years, median (IQR)	32.0 (27.0-36.0)	31.0 (27.0-35.0)	0.035
Body mass index in kg/m^2, median (IQR)	27.1 (23.6-31.83)	23.9 (21.4-27.7)	<0.001
Nulliparous, n (%)	206 (59.7)	3442 (68.4)	0.001
Pregnancy outcome			0.266
Livebirth, n (%)	384 (99.5)	4916 (99.8)	
Stillbirth, n (%)	2 (0.5)	8 (0.2)	
Perinatal death, n (%)	0 (0)	3 (0.1)	
Gestational age at delivery in weeks, median (IQR)	39.0 (37.14-40.43)	40.14 (39.0-41.14)	<0.001
Birthweight centile, median (IQR)	29.30 (7.53-57.08)	38.13 (17.09-63.85)	<0.001
Small for gestational age, n (%)	110 (28.7)	740 (15.2)	<0.001
Second trimester uterine artery (UtA) mean pulsatility index (PI) MoM, median (IQR)	0.84 (0.69-1.06)	0.77 (0.64-0.96)	<0.001
Third trimester UtA mean PI MoM, median (IQR)	0.76 (0.611-1.02)	0.67 (0.57-0.81)	<0.001
Difference between the third and second UtA mean PI MoM, median (IQR)	-0.07 (-0.32-0.20)	-0.09 (-0.31-0.09)	0.010

Table 3. Logistic regression analysis for the prediction of hypertensive disorders in pregnancy (HDP) using maternal age, body mass index (BMI), Afro-Caribbean ethnicity, difference between the third and second trimester uterine artery (UtA) mean pulsatility index (PI) multiple of the median (MoM), third trimester uterine artery MoM and estimated fetal weight (EFW) centile

	Adjusted odds ratio (OR)	**95% confidence interval**	**P value**
Maternal age	1.01	0.994-1.03	0.179
BMI	1.08	1.06-1.09	<0.001
Black ethnicity	1.37	1.04-1.81	0.023
Stable/Decrease in UtA PI between 2nd and 3rd trimester	0.43	0.31-0.60	<0.001
Third trimester UtA PI	7.35	4.66-11.60	<0.001
EFW centile	0.994	0.990-0.998	0.005