Fetal Diagnosis and Therapy

Effect of Chorionic Villus Sampling on Uterine Artery Doppler

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Abstract

Introduction: The aim of this study was to examine the potential effect of chorionic villus sampling (CVS) on placental perfusion by examining the change in uterine artery pulsatility index (PI) between the first and second trimesters of pregnancy. *Materials and Methods:* This was a prospective screening study for pregnancy complications which included measurement of uterine artery PI at 11^{+0} to 13^{+6} weeks and at 20^{+0} to 24^{+6} weeks of gestation. In women at increased risk for fetal aneuploidies, CVS was performed. Uterine artery PI in the first and second trimesters, and the change in PI between the two examinations were compared between the CVS and non-CVS groups. *Results:* The study population included 8,822 singleton pregnancies, in 308 of which CVS was performed. In the CVS group, compared to the non-CVS group, the median uterine artery PI before CVS, corrected for gestational age, was higher in both the first and second trimesters of pregnancy, but the change in PI between the two examinations was not significantly different (p = 0.789). *Conclusion:* The performance of CVS in the first trimester is unlikely to interfere with normal placentation.

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Introduction

Chorionic villus sampling (CVS) is associated with placental damage with consequent miscarriage in around 1% of cases [1, 2]. There is also some evidence that the CVS-related placental damage can cause fetal limb reduction defects when the procedure is performed before 10 weeks of gestation [3]. Some studies reported that CVS is associated with an increased risk of subsequent development of preeclampsia (PE) [4–7] and suggested that this might be related to placental damage caused by the invasive procedure. Suggested mechanisms for such an association include the following CVS-related consequences: (a) focal placental hemorrhage and inflammation resulting in reduced placental perfusion, (b) release of paternally derived fetal antigens stimulating a maternal immune response and endothelial dysfunction, and (c) alteration in the balance of angiogenic and antiangiogenic placental products, such as PlGF, VEGF and sFlt-1, which are known to play a role in the pathophysiology of PE [5, 6, 8].

Extensive evidence suggests that PE is a consequence of impaired trophoblastic invasion of the maternal spiral arteries and their physiological conversion into large non-muscular low-resistance channels [9, 10]. Such impairment is reflected in increased pulsatility index (PI) in

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the waveforms obtained from the uterine arteries by Doppler ultrasound [11–13]. In normal pregnancies uterine artery PI decreases between the first and second trimesters, but this fall is less in pregnancies that develop PE [14, 15]. One study investigated the short-term effect of CVS on uterine artery PI and reported that in 17 women undergoing CVS there was no significant change in PI measured before and at 10 and 60 min after the procedure [16].

The aim of this study was to investigate the potential long-term effects of CVS on placental perfusion by examining the change in uterine artery PI between the first and second trimesters of pregnancy.

Materials and Methods

This was a prospective screening study for pregnancy complications which included measurement of uterine artery PI at 11^{+0} to 13^{+6} weeks and at 20^{+0} to 24^{+6} weeks of gestation. The study was approved by the King's College Hospital Ethics Committee and all participants gave their written informed consent. The entry criteria for this study were a singleton pregnancy with a live fetus at 11^{+0} to 13^{+6} weeks and surviving to beyond 23 weeks of gestation and who had measurements of uterine artery Doppler at 11^{+0} to 13^{+6} weeks and at 20^{+0} to 24^{+6} weeks. We excluded pregnancies resulting in miscarriage, those with fetal aneuploidies or major defects, terminations for psychosocial reasons, those with unknown pregnancy outcome and those who had an amniocentesis.

In the first trimester, women had combined screening for chromosomal abnormalities which involved an ultrasound scan to measure fetal crown-rump length (CRL) and nuchal translucency (NT) thickness, and measurement of maternal serum concentration of pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG; Delfia Xpress Analyzer; Perkin Elmer Life and Analytical Sciences, Waltham, Mass., USA). The results of maternal age, fetal NT, and serum free β-hCG and PAPP-A were used to estimate the patient-specific risk for trisomy 21 [17, 18]. Gestational age was determined from the measurement of fetal CRL [19]. Women identified as being at high risk of chromosomal defects were offered CVS for fetal karyotyping. In all cases, CVS was performed after the measurement of uterine artery PI. The method of CVS was transabdominal and involved the ultrasound-guided insertion into the placenta of an 18-G needle after the administration of local anesthesia (lidocaine 1%) to the abdominal wall.

In the second trimester, a detailed ultrasound examination was carried out for assessment of fetal growth and the diagnosis of major fetal defects. Uterine artery Doppler was performed in both the first- and second-trimester scans. In the first trimester, a sagittal section of the uterus was obtained and the cervical canal and the internal cervical os was identified, as previously described [20]. The transducer was then gently tilted from side to side and color-flow mapping was used to identify each uterine artery adjacent to the cervix and uterus at the level of the internal os. Pulsed wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle

of insonation was less than 30°. When three similar consecutive waveforms were obtained, the PI was measured and the mean PI of the left and right arteries calculated. In the second trimester, the mean uterine artery PI was measured transvaginally because, at the same time, we measured cervical length to assess the risk of preterm delivery. All Doppler studies were carried out by sonographers who had received the Certificate of Competence in Doppler of the Fetal Medicine Foundation (www.fetalmedicine.com).

The ultrasound findings and patient characteristics, including demographic data and obstetric and medical history, were entered into a computer database. At the first trimester visit, women were asked to complete a questionnaire on age, racial origin (Caucasian, African, South Asian, East Asian or mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous, assisted), medical history of chronic hypertension (yes or no), parity (parous or nulliparous – if no delivery beyond 23^{+6} weeks), obstetric history (including previous pregnancy with PE) and family history of PE in the mother (yes or no). The questionnaire was then reviewed by a doctor together with the woman. The maternal weight and height and body mass index were measured.

Data on pregnancy outcomes were obtained from the computerized maternity unit records.

Statistical Analysis

Maternal and fetal characteristics in the CVS and non-CVS groups were compared using the χ^2 test for categorical variables and the Mann-Whitney test for continuous variables. The data on uterine artery mean PI were made Gaussian after logarithmic transformation. Regression analysis was used to determine the significance of the association between uterine artery mean PI and gestational age in both the first and second trimesters. Delta values of first- and second-trimester mean PIs for each patient were then calculated as the difference from the expected mean for gestation. The ratio of the delta value of mean PI in the second trimester to the delta value in the first trimester was calculated for each patient. The Mann-Whitney test was used to determine the significance of differences in the median delta ratios of the CVS and non-CVS groups.

Multiple regression analysis was used to determine whether CVS had a significant contribution in predicting uterine artery PI in addition to maternal and pregnancy characteristics. The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analysis.

Results

During the study period (March 2006 to August 2009), uterine artery Doppler at both 11^{+0} to 13^{+6} and 20^{+0} to 24^{+6} weeks of gestation was performed in 9,340 women but 518 were excluded from the study because they had amniocentesis (n = 63), fetal aneuploidies or major defects (n = 18), they resulted in miscarriage (n = 10), or the pregnancy outcome was unknown (n = 427). We included 8,822 cases and in 308 of these CVS was performed. In the CVS group, 12 women (3.9%) developed PE compared with 283 women (3.3%) in the non-CVS group.

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Table 1. Maternal and pregnancy characteristics in the CVS and non-CVS groups

Maternal and pregnancy characteristics	Non-CVS group (n = 8,514)	CVS group (n = 308)
Maternal age in years, median (IQR)	31.6 (27.2–35.3)	35.5 (30.9–39.8)*
Body mass index, median (IQR)	24.2 (21.9–27.6)	24.2 (21.7–26.9)
Gestation at screening (days), median (IQR)	12.7 (12.3–13.1)	12.7 (12.3–13.2)
Racial origins, n (%)		
Caucasian	4,837 (56.8)	201 (65.3)
African	2,832 (33.3)	74 (24.0)*
South Asian	354 (4.2)	13 (4.2)
East Asian	159 (1.9)	12 (3.9)*
Mixed	332 (3.9)	8 (2.6)
Parity, n (%)		
Nulliparous	4,529 (53.2)	135 (43.8)
Parous – no previous PE	3,702 (43.5)	158 (51.3)*
Parous – previous PE	283 (3.3)	15 (4.9)
Family history of PE, n (%)	379 (4.5)	9 (2.9)
Cigarette smoker, n (%)	589 (6.9)	19 (6.2)
Conception, n (%)		
Spontaneous	8,214 (96.5)	275 (89.3)
Assisted conception	300 (3.5)	33 (10.7)*
History of chronic hypertension, n (%)	132 (1.6)	7 (2.3)
Serum PAPP-A MoM, median (IQR)	1.04 (0.72–1.47)	0.64 (0.36–1.05)*
Serum free β-hCG MoM, median (IQR)	1.00 (0.68–1.51)	1.14 (0.74–2.14)*
Development of PE, n (%)	283 (3.3)	12 (3.9)
Gestation at delivery in weeks, median (IQR)	39.6 (38.7–40.6)	40.0 (39.0–40.9)

Comparisons between outcome groups (χ^2 test for categorical variables and Mann-Whitney test for continuous variables): * $p < 0.05$.

Table 2. Median and interquartile range of uterine artery mean PI in the first and second trimesters of pregnancy in the CVS and non-CVS groups

Uterine artery PI	Non-CVS group (n = 8,514)	CVS group (n = 308)
Uterine artery PI – first trimester		
Delta value	0.03 (–0.26 to 0.38)	0.14 (–0.18 to 0.53)*
Raw value	1.64 (1.33 to 1.99)	1.72 (1.42 to 2.12)*
Uterine artery PI – second-trimester		
Delta value	0.00 (–0.16 to 0.19)	0.07 (–0.10 to 0.25)*
Raw value	1.03 (0.87 to 1.22)	1.10 (0.92 to 1.27)*
Delta second trimester/delta first trimester	0.27 (–0.22 to 0.75)	0.26 (–0.23 to 0.78)

Comparisons between groups by the Mann-Whitney test: significance value * $p < 0.05$.

The maternal and pregnancy characteristics of the CVS and non-CVS groups are compared in table 1. In the CVS group, the median maternal age was higher, there were fewer women of African racial origin, more women had assisted conception, the median maternal serum PAPP-A was lower and free β-hCG was higher.

In the CVS group, compared to the non-CVS group, the median delta uterine artery mean PI was higher in both the first and second trimesters of pregnancy (table 2). However, multiple regression analysis demonstrated that CVS did not have a significant contribution in predicting uterine artery PI in addition to maternal and

Table 3. Multiple regression analysis to determine the maternal and pregnancy characteristics contributing significantly to the prediction of log uterine artery mean PI in the first and second trimesters of pregnancy

Characteristic	Coefficient	t statistic	p value	95% CI
First trimester				
Maternal age	−0.001	−3.850	<0.0001	−0.001 to 4.5e-04
Body mass index	−0.002	−5.633	<0.0001	−0.002 to −0.001
African racial origin	0.029	9.352	<0.0001	0.023 to 0.035
Mixed racial origin	0.025	3.564	<0.0001	0.011 to 0.039
Gestational age	−0.029	−12.163	<0.0001	−0.033 to −0.024
log PAPP-A MoM	−0.084	−14.692	<0.0001	−0.094 to −0.073
Second trimester				
Maternal age	−4.2e-04	−2.086	0.037	−8.2e-04 to −2.5e-05
Body mass index	7.1e-04	2.939	0.003	2.3e-04 to 0.001
Smoking status	0.012	2.556	0.011	0.003 to 0.020
African racial origin	0.017	6.293	<0.0001	0.012 to 0.022
South Asian racial origin	−0.015	−2.539	0.011	−0.026 to −0.003
East Asian racial origin	−0.023	−2.871	0.004	−0.040 to −0.008
Gestational age	−0.010	−5.782	<0.0001	−0.013 to −0.006
log PAPP-A MoM	−0.090	−18.49	<0.0001	−0.099 to −0.080
log free β-hCG MoM	−0.023	−5.184	<0.0001	−0.031 to −0.008

pregnancy characteristics (table 3). In the first trimester, the following factors made a significant contribution to the prediction of log uterine artery PI: maternal age, BMI, African and mixed racial origin, gestational age, and log PAPP-A MoM, but the following factors did not: smoking status (p = 0.065), assisted conception (p = 0.468), delta NT (p = 0.573), log free β-hCG MoM (p = 0.344), and CVS (p = 0.059). In the second trimester, the following factors made a significant contribution to the prediction of log uterine artery PI: maternal age, BMI, smoking status, African, South Asian and East Asian racial origin, gestational age, log PAPP-A MoM, and log free β-hCG MoM, but the following factors did not: delta NT (p = 0.391) and CVS (p = 0.361).

In the CVS group, compared to the non-CVS group, the median delta uterine artery mean PI was higher in both the first and second trimesters of pregnancy, but the ratio of delta PI in the second to the first trimester was not significantly different (p = 0.789, table 2).

Discussion

The results of our study demonstrate that the performance of CVS in the first trimester has no significant effect on the change in uterine artery mean PI between the first and second trimesters of pregnancy. These findings do not support the hypothesis that CVS leads to placental disruption and alteration in placental perfusion that is detectable by uterine artery Doppler.

Some studies reported that the incidence of PE in women having CVS is higher than in controls who had either amniocentesis or no invasive test and this led to the suggestion that CVS contributes to the development of PE [4–7]. A more likely explanation for this association is that the same components of screening leading to increased risk for chromosomal defects and therefore the uptake of CVS, such as increased maternal age and decreased serum PAPP-A, are also associated with increased risk of PE [21]. As shown in this study, in the CVS group compared to the non-CVS group, the uterine artery PI was higher in both the first trimester before the CVS and in the second trimester of pregnancy, and this increase was due to maternal and pregnancy characteristics, rather than to the invasive procedure per se. The women in the CVS group were older and had lower serum PAPP-A, factors which are known to be associated with increased uterine artery PI [22].

In normal pregnancy, trophoblastic invasion of the maternal spiral arteries continues during both the first and second trimesters and this is reflected in a fall in uterine artery PI with gestation which reaches a plateau at around 24 weeks [11–13, 23]. In women with impaired placentation, who are therefore at increased risk of developing PE, there is attenuation of the normal fall in uterine artery PI from the first to the second trimester [14, 15].

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Our study demonstrates that CVS is not associated with such attenuation of the fall in uterine artery PI with gestation. We conclude, therefore, that a CVS procedure in the first trimester is unlikely to interfere with normal placentation.

Acknowledgment

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