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CLINICAL ARTICLE

Association between maternal vascular murmur and the small-for-gestational-age fetus with abnormal umbilical artery Doppler flow

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Keywords: Arterial sound analysis; Intrauterine growth restriction; Maternal vascular murmur; Prenatal monitoring; Umbilical artery flow; Uterine artery flow

Synopsis: Maternal vascular murmurs are significantly associated with fetal growth restriction, but not with small for gestational age per se.

Abstract

Objective: To investigate the association between maternal vascular murmurs (MVMs) and fetal growth restriction (defined as small-for-gestational-age [SGA] fetus) and abnormal Doppler pulsatility index (PI) of the uterine and/or umbilical arteries.

Methods: A cross-sectional study of women aged 18 years or older with a singleton pregnancy at 28–34 weeks was conducted at Regional Hospital Viborg, Denmark, between May 1 and August 1, 2013. Ultrasound fetal biometry was performed and the Doppler PI of the umbilical and uterine arteries was determined. An estimated fetal weight (EFW) at or below the 10th percentile was defined as SGA. Microphone recordings from the lower abdomen were divided into heart valve sounds and MVMs.

Results: The final analysis included 63 participants, with 25 classified as SGA and 38 as non-SGA. The mean pregnancy duration was 32.4 ± 1.4 weeks. In total, 17 participants had MVMs. There was a clear association between MVMs and a composite of SGA and an abnormal PI of the uterine and/or the umbilical artery (P<0.001), but not between MVMs and SGA only (P=0.154).

Conclusion: Maternal vascular murmurs are significantly associated with fetal growth restriction, but not with SGA per se.

1 INTRODUCTION

The main cause of fetal growth restriction (FGR) is compromised placental function. However, more than half of fetuses considered small for gestational age (SGA; defined as an estimated fetal weight [EFW] <10th percentile) are in fact constitutionally small [1]. It remains a clinical challenge to identify fetuses at risk of adverse outcome so that prenatal monitoring can be targeted accordingly. The initial identification of a growth-restricted fetus depends on the long-standing discrepancy in whether to rely on standardized or population-based growth charts when fetal weight is estimated by ultrasound biometry [2,3]. Still, when SGA is diagnosed, discrepancies in the diagnostic criteria and definitions on FGR complicate the clinical management. Unterscheider et al. [4] showed that the prediction of adverse fetal outcomes could be optimized by using a combination of EFW below the 10th percentile and abnormal umbilical artery velocimetry.

There is a need to optimize the timely identification of SGA fetuses as a proxy for FGR fetuses because more than half of all SGA fetuses are not identified before birth [5,6]. The ability to distinguish a healthy fetus with a normal or low weight from a compromised fetus is not only critical in the clinical context, but is also important as a source of preclinical information: in the long term, the fetal response to placental dysfunction is associated with comorbidities such as cardiovascular and metabolic diseases [7,8].

The maternal vascular murmur (MVM) is a new acoustic marker of disturbed maternal vascular flow [9–11] that is currently being investigated in the prenatal clinical context. The hypothesis of the present study was that MVM could be used to

identify fetuses compromised by placental dysfunction attributable to abnormal spiral artery modification. If the spiral arteries fail to remodel to accommodate pregnancy, this leaves non-dilated vessels with retained endothelium and smooth muscle, which in turn is associated with placental lesions and adverse pregnancy outcomes and is found at a prevalence of approximately 6% [12]. The use of vascular murmurs as an acoustic marker for the diagnosis of disturbed arterial flow is not novel: these pulsatile high-frequency sounds are known to be generated in patients with carotid, femoral, or coronary stenosis when the blood flow becomes turbulent distally to a reduction in the arterial lumen [13–15]. However, this occurrence has yet to be investigated in an obstetric context.

The aim of the current study was to investigate the potential association between MVMs and early-onset FGR, defined as a composite of an ultrasound-defined EFW at or below the 10th percentile for the given gestational age and an abnormal umbilical and/or uterine artery blood flow.

2 MATERIALS AND METHODS

The present observational, cross-sectional study included all women aged 18 years or more with a singleton pregnancy at 28–34 weeks who were seen at the Prenatal Care Unit at the Regional Hospital in Viborg, Denmark, between May 1 and August 1, 2013. The pregnancy duration was established on the basis of the routine ultrasonography examination at 10–12 weeks offered as part of the Danish national prenatal program. Exclusion criteria were pre-eclampsia (blood pressure >140/90 mm Hg and proteinuria), pregnancy-induced hypertension (blood pressure <140/90 mm Hg without proteinuria), gestational diabetes mellitus, body mass index

(BMI; calculated as weight in kilograms divided by the square of height in meters) of greater than 35, and absent ultrasonography at 10–12 weeks. The Ethics Committee of Northern Jutland, Denmark, approved the study protocol. Written informed consent was obtained from all participants.

Data on the maternal brachial blood pressure, pulse, BMI, age, parity, and the occurrence of emergency interventions (maternal prophylactic betamethasone injection or emergency cesarean delivery within 1 hour of the Doppler ultrasound examination) were recorded.

After recruitment, ultrasound biometry was performed to determine the biparietal diameter of the fetal head, the head circumference, the abdominal circumference, and the femur length. Fetuses with an EFW at or below the 10th percentile with reference to a conventional population-based growth standard were diagnosed as SGA; fetuses with an EFW above the 10th percentile were characterized as appropriate for gestational age (AGA). Additionally, an abdominal Doppler ultrasonography examination of the uterine arteries and the umbilical artery was performed. Fetal growth restriction was defined as SGA and an abnormal pulsatility index (>95th percentile) of the umbilical artery [16].

Following the ultrasonography study, 180 seconds of acoustic recordings of arterial sound were obtained using four abdominal microphones placed above the lower part of the uterus (Figure 1) and one thoracic microphone placed in the left fourth to fifth intercostal space near the left sternal border. The acoustic recordings were obtained using 4060 Danish Pro Audio microphones (DPA Microphones, Alleroed, Denmark);

RME Fireface 800 (RME, Haimhausen, Germany), a multichannel, 24-bit, 192-kHz FireWire audio interface; and Matlab R2041b (Mathworks, Natick, MA, USA) on a connected computer.

An examiner who was masked to all baseline data analyzed the vascular sound recordings by visually examining whether the raw signal (frequency 25–3000 Hz) contained a pulsatile pattern that was consistent with the maternal heart rate obtained by the thoracic microphone. This procedure was done for all four microphones. If no such pulsatile pattern was identified, the recording was excluded, and if more than two of the four abdominal recordings were excluded, the participant was excluded. In the recordings of the remaining participants, the pulsatile pattern consistent with the maternal heart rate was searched for in the spectrum of 200–800 Hz. If the pulsatile pattern also occurred within this particular spectrum, the recording was classified as containing MVMs (Figure 2, upper graph) [11]. If none of the recordings from a participant contained MVMs (Figure 2, lower graph), the participant was placed in the non-MVM group.

Statistical tests were performed using SPSS version 24 (IBM, Armonk, NY, USA). The Levene test for homogeneity of variance was performed on the demographic and outcome variables, and parametric (*t* test) or nonparametric (Mann-Whitney *U* test) tests were applied as appropriate. Additionally, contingency table analysis, including sensitivity and specificity analyses, and Fisher exact test were applied. $P \leq 0.05$ was considered statistically significant.

3 RESULTS

The study included 80 women with singleton pregnancies. Mean pregnancy duration was 32.5 ± 1.4 weeks. Overall, 34 women had an SGA fetus and 46 had an AGA fetus. On initial characterization of the sound recordings, 17 (21%) participants were excluded because no pulsatile pattern consistent with the maternal heart could be identified, leaving 63 participants for further investigation. Of these, 25 (40%) participants had an SGA fetus and 38 (60%) had an AGA fetus.

The ethnicity distribution was as follows: African (n=2 [3%]), Asian (n=5 [8%]), Middle Eastern (n=6 [10%]), South American (n=1 [2%]), and European (n=49 [78%]). The mean maternal age was 28.6 ± 6.3 years, the median parity was 1 ± 2, and the mean pregnancy duration was 32.4 ± 1.4 weeks. The mean BMI was 25.8 ± 3.5. The systolic blood pressure was 134 ± 25 mm Hg and the diastolic blood pressure was 80.6 ± 13 mm Hg. The mean maternal pulse was 83 ± 16 beats per minute.

The mean uterine artery Doppler PI was 0.94 ± 0.40 and the mean umbilical artery PI was 0.99 ± 0.24. In 15 (24%) women, emergency interventions were performed within 1 hour of the Doppler ultrasonography examination.

Of the 63 participants, 17 (27%) had MVMs. The differences between the MVM and non-MVM groups in EFW and SGA were not significant (Table 1). The main pregnancy and demographic variables—pregnancy duration, parity, maternal age, blood pressure, and BMI—also showed no significant association with the MVM and non-MVM categorization (Table 1).

By contrast, MVM was significantly associated with pregnancies complicated by a composite of SGA and an abnormal PI of the umbilical artery, the uterine artery, or both arteries (all $P \leq 0.001$) (Table 1). Similarly, MVM was significantly associated with emergency intervention ($P=0.009$) (Table 1).

Testing the distribution frequencies using the Fischer exact test showed that MVM had a poor sensitivity (0.36) for the identification of SGA fetuses, with a specificity of 0.79 (Table 2); the association was not significant ($P=0.154$). However, when the MVM marker was tested for the identification of pregnancies complicated by SGA and an abnormal umbilical artery PI, the sensitivity was 0.85, the specificity was 0.88, and the association was significant ($P<0.001$) (Table 3). The sensitivity and specificity values for the detection of pregnancies complicated by SGA and an abnormal uterine artery PI were 0.56 and 0.83, respectively ($P=0.004$) (Table 4). For the detection of pregnancies complicated by SGA and an abnormal Doppler PI in both arteries, the sensitivity and specificity values were 1.00 and 0.82, respectively ($P<0.001$) (Table 5).

4 DISCUSSION

To the best of our knowledge, the present study was the first to investigate the relationship between MVM and early-onset FGR. The findings indicate significant associations between the MVM marker and pregnancies complicated by SGA and abnormal blood flow in the umbilical and uterine arteries.

The MVM marker was originally discovered by separating the raw pulsatile sound signal obtained by abdominal microphones adjacent to the uterine arteries into two

frequency segments [11]. At the lower frequency (25–100 Hz), cardiac sounds were audible and visible with distinct delimitations of a first valve sound caused by closure of the atrioventricular valves and a second valve sound caused by closure of the semilunar valves. In the higher frequency segment (200–800 Hz), a consistent pulsatile bruit or murmur (MVM) could be obtained [11]. The existence of vascular murmurs in this frequency segment has previously been associated with turbulent flow distal to a reduced arterial passage in cardiovascular disease [13–15]. Given that the investigation of vascular murmurs is new in the context of pregnancy, and given the lack of consensus on the best method to identify FGR [6], we chose to evaluate the relationship between MVM and FGR as defined on the basis of findings from a prospective multicenter study [4] that was conducted to identify the prenatal sonographic method that was most strongly associated with an adverse neonatal outcome in pregnancies complicated by growth restriction. Researchers worldwide have called for consensus on the terminology and definition of FGR, the method of identification, and the composite outcome measures used in this fast-moving field of research [5,6,17–19], and substantial efforts are being made in clinical practice to establish these parameters [20,21]. Early-onset FGR, as investigated in the present study (pregnancy duration 28–34 weeks), is of particular concern because the risk of iatrogenic prematurity and comorbidities is considerable [22].

In view of the present finding that MVM was significantly associated with FGR but not with constitutional SGA, further investigation is called for because clinical management independent of the use of ultrasound biometry and the risk of systematic errors by the use of standard references is of considerable potential [1–3]. Additionally, given that MVM was significantly associated with the performed

interventions as part of the standard clinical management in a Scandinavian hospital setting, research into the relationship between MVM and early- versus late-onset FGR is needed to establish the potential use of the marker as part of diagnostics.

In the present study, the MVM marker performed with the best precision in the identification of abnormal flow in the umbilical artery, although the information imbedded in the vascular sound is indeed maternal. This finding supports the working hypothesis that the disrupted pre-placental and/or uteroplacental blood flow affecting placental function is audible and that the turbulent marker correlates with the known adverse outcome as established by extensive research [5,7,23,24]. However, caution must be used: the exact (patho)physiological origin of the murmur is yet to be defined.

The limitations of the present study include the definition of FGR as EFW at or below the 10th percentile and an abnormal umbilical artery PI, and the lack of perinatal and neonatal outcome measures verifying the FGR diagnosis. The latter would have been important to help differentiate constitutional SGA and pathological FGR. However, MVM was compared with two of the standard tools used in the clinical diagnosis of FGR—the ultrasound-defined EFW and the Doppler flow measure.

Another limitation is the fact that the study population was highly selected, which could affect the external validity of the study. In future studies, it will be important to confirm the findings in an unselected population. Moreover, the microphone positions have to be confirmed in a large heterogeneous population because differences in the pregnancy duration and anthropometric data could influence the quality of the sound

signal. In the current study, ethnic diversity was moderate given that more than 75% of the women were of European origin. The exclusion of 21% of the recruited participants because of unacceptable sound signal quality warrants further investigation of the recording strategy, particularly with regard to the microphone positions and anthropometric differences.

We tried to maximize the internal validity by including participants with singleton pregnancies and comparable pregnancy duration and parity. The Levene test performed on the demographic variables (maternal age and parity) also showed reliable homogeneity of variance. The clinical baseline variables (the maternal systolic and diastolic blood pressure and, importantly, the EFW) were not significantly different between the MVM and non-MVM groups.

The study design was observational, exploratory, and cross-sectional because the causal relation of this novel marker with an adverse outcome has yet to be determined and possible confounding factors are still unknown. In the present study, the maternal BMI and blood pressure were included as variables to establish whether MVM is associated with these factors. The maternal BMI might be relevant because the extent of abdominal fat could affect sound signal transmission, and the maternal blood pressure could be of importance because of its relationship with comorbidities such as pre-eclampsia and pregnancy-induced hypertension [25]. A future prospective cohort study should investigate the MVM marker and its association with early and late clinical correlates of placental dysfunction including prenatal, perinatal, and neonatal outcome measures, and importantly also histological investigations of placental tissue.

In conclusion, the present findings show that MVM as a marker of maternal vascular flow disturbance is significantly associated with an abnormal PI in both the umbilical artery and the uterine artery in SGA fetuses. The marker is, however, not significantly associated with SGA without any accompanying flow changes in the umbilical or uterine artery.

Author contributions

DR was the main contributor to the present work. DR was involved in the preparation of the study, obtained ethics approval, collected and analyzed the data, and prepared the manuscript. RF participated in the preparation and conduction of the study as the principal investigator. RF also contributed to the data interpretation and the writing and critical review of the manuscript. MH contributed to the design of the study, the data interpretation, intellectual discussions, and the review of the manuscript. PH participated in the data analysis and interpretation, provided advice on clinical aspects of the methods, and contributed to the writing and final revision of the manuscript. JJS supervised DR throughout the entire project, and participated in the design of the study, the data interpretation, and the writing and revision of the manuscript. All authors approved the final version of the manuscript.

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Conflicts of interest

DR was partly funded by Viewcare, Herlev, Denmark, as an Industrial PhD student. The other authors have no conflicts of interest.

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Figure legends

Figure 1 Setup for the recording of vascular sounds from the lower abdomen: two microphones were placed bilaterally on the abdomen. One at the position of the uterine artery crossing the internal iliac artery as identified by the uterine artery Doppler scans and one medially between this position and the abdominal midline. The setup was used bilaterally on the abdomen on both uterine arteries.

Figure 2 Time–frequency representation of a 30-second sound recording. The upper graph illustrates a recording with a pulsatile pattern reaching a frequency of approximately 800 Hz (maternal vascular murmur), and the lower graph illustrates a recording without a pulsatile pattern.

Table 1 Clinical variables by MVM status (n=63).[a]

Variable	**MVM (n=17)**	**No MVM (n=46)**	***P* value**
Maternal age, y	28 ± 5	28 ± 3	0.842 [b]
Parity	0 ± 2	1 ± 1	0.413 [b]
Pregnancy duration, w	32.0 ± 1.6	32.5 ± 1.2	0.130 [b]
Systolic blood pressure, mm Hg	133 ± 20	134 ± 27	0.851 [b]
Diastolic blood pressure, mm Hg	81 ± 12	80 ± 13	0.914 [b]
Body mass index [c]	25.6 ± 3.0	26.0 ± 4.1	0.472 [b]
Estimated fetal weight, g	1702 ± 399	1849 ± 332	0.146 [b]
SGA	9	16	0.195 [d]
SGA and abnormal umbilical artery PI	11	2	<0.001 [d]
SGA and abnormal uterine artery PI	9	7	0.001 [d]
SGA and abnormal umbilical artery and uterine artery PI	7	0	<0.001 [d]
Interventions	9	6	0.009 [d]

Abbreviation: PI, pulsatility index.
[a] Values are given as mean ± SD or number, unless indicated otherwise.
[b] Independent *t* test.
[c] Calculated as weight in kilograms divided by the square of height in meters.
[d] Mann–Whitney *U* test.

Table 2 Contingency table for the association between MVM and pregnancies complicated by SGA (n=63).

Presence of MVM	**SGA: condition positive**	**SGA: condition negative**
Test outcome positive	TP = 9 FP = 16	FN = 8 TN = 30
Sensitivity	9/(9+16) = 0.36	–
Specificity	–	30/(30+8) = 0.79

Abbreviations: MVM, maternal vascular murmur; SGA, small for gestational age; TP, true positive; FN, false negative; FP, false positive; TN, true negative.

Table 3 Contingency table for the association between MVM and pregnancies complicated by SGA and an abnormal umbilical artery PI (n=63).

Presence of MVM	**SGA and abnormal umbilical artery PI: condition positive**	**SGA and abnormal umbilical artery PI: condition negative**
Test outcome positive	TP = 11 FP = 2	FN = 6 TN = 44
Sensitivity	11/(11+2) = 0.85	–
Specificity	–	44/(44+6) = 0.88

Abbreviations: MVM, maternal vascular murmur; SGA, small for gestational age; PI, pulsatility index, TP, true positive; FN, false negative; FP, false positive; TN, true negative.

Table 4 Contingency table for the association between MVM and pregnancies complicated by SGA and an abnormal PI of the uterine artery (n=63).

Presence of MVM	**SGA and abnormal uterine artery PI: condition positive**	**SGA and abnormal uterine artery PI: condition negative**
Test outcome positive	TP = 9 FP = 7	FN = 8 TN = 39
Sensitivity	9/(9+7) = 0.56	–
Specificity	–	39/(39+8) = 0.83

Abbreviations: MVM, maternal vascular murmur; SGA, small for gestational age; PI, pulsatility index; TP, true positive; FN, false negative; FP, false positive; TN, true negative.

Table 5 Contingency table for the association between MVM and pregnancies complicated by SGA and abnormal PIs of the umbilical and uterine arteries (n=63).

Presence of MVM	**SGA and abnormal umbilical and uterine artery PI: condition positive**	**SGA and abnormal umbilical and uterine artery PI: condition negative**
Test outcome positive	TP = 7 FP = 0	FN = 10 TN = 46
Sensitivity	7/(7+0) = 1.00	–
Specificity	–	46/(46+10) = 0.82

Abbreviations: MVM, maternal vascular murmur; SGA, small for gestational age; PI, pulsatility index; TP, true positive; FN, false negative; FP, false positive; TN, true negative.