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ORIGINAL RESEARCH

Ultrasound visualization and blood flow velocity measurements of the adrenal arteries in the fetus

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Abstract

Introduction: Detection and surveillance of fetal growth restriction (FGR) is well established, but there is still room for improvement. Animal studies indicate that compromised fetuses increase adrenal blood flow. Modern ultrasound equipment allows us to measure vascular impedance in the fetal adrenal arteries despite their modest size. However, extensive anatomical variance is a challenge to standardizing measurements. We set out to improve this.

Material and Methods: We included 75 low-risk pregnant women in a prospective cross-sectional study aiming to develop a reliable technique to visualize and measure flow velocity in human fetal adrenal arteries. We used commercially available ultrasound equipment: a GE Voluson 10 2019 with a C2-9 probe (GE Healthcare, Zipf, Austria), and a Philips Epiq Elite with a V9-2 probe (Philips Medical Systems International B.V., Best, The Netherlands), exploiting the modern sensitive power Doppler modes in both scanners to visualize small vessels.

Results: Among 72 fetuses, the inferior adrenal artery was the most consistently visualized and measured artery to the gland. Doppler velocimetry was achieved in 66 (92%) participants. We found the anatomical variation described previously but were able to develop visualization strategies to identify the common arteries and use a consistent Doppler technique for the second half of pregnancy.

Conclusions: It is possible to visualize and measure flow velocity in the adrenal arteries of human fetuses. The success rate was highest for the inferior adrenal artery making this vessel a candidate for clinical studies.

KEYWORDS
adrenal arteries, Doppler ultrasound, fetal growth restriction, placental dysfunction, suprarenal arteries

Abbreviations: FGR, Fetal growth restriction; PI, Pulsatility index.

1 | INTRODUCTION

Placental dysfunction and subsequent fetal growth restriction (FGR) is a leading cause of perinatal mortality and morbidity worldwide.[1–3] The current standard of diagnosing FGR is by estimating fetal size and growth by ultrasound and using Doppler velocimetric evaluations to look for signs of placental dysfunction and fetal compromise.[4] In both the diagnostic workup and when monitoring a fetus with established FGR, Doppler evaluation of the blood flow in the umbilical artery and the fetal middle cerebral artery are central parts of the evaluation, alongside computerized cardiotocography and Doppler velocimetry of the ductus venosus.

Limitations in the current diagnostic and monitoring approach carry a risk of harmful under- and overtreatment. International guidelines concerning diagnosis and management of FGR call for more research into new tools to improve these strategies.[5,6] Animal studies have shown increased adrenal blood flow in fetuses under experimentally induced placental dysfunction.[7] Indeed, these studies often show the adrenal glands to be the fetal organ that exhibits the relatively largest increase in blood flow during such experiments. As Doppler lets us measure blood flow velocities, examination of the adrenal arteries with Doppler ultrasound has the potential to become a useful additional clinical tool. Similar studies of other organs have spurred the development of diagnostic procedures that are now implemented into clinical practice, such as Doppler measurements of the middle cerebral artery and the ductus venosus.[8,9]

Previous attempts to develop Doppler of the adrenal arteries as a diagnostic and prognostic tool for FGR have not proven conclusive.[10–13] This may be due to limitations in previous generations of ultrasound equipment in assessing blood flow velocity in vessels of such small caliber. The abundance of other small arteries in the region, such as the intercostal arteries, and the lack of consensus on how to perform Doppler measurements in the adrenal arteries, may also have impeded the introduction into clinical practice.

The adrenal glands receive their blood supply from the inferior adrenal artery, middle adrenal artery, and inferior phrenic arteries. There is considerable anatomical variation in their origin, numbers, and topographic course of the vessels.[14–20] There is a lack of consensus on how to define the different arteries. The Federative International Programme for Anatomical Terminology (FIPAT) uses the origin of the vessel as defined in its publication "Terminologia Anatomica".[21] Most authors, however, define the adrenal arteries based on which area of the gland they supply,[14,17–19] and yet others do not specify.[15,16,22,23]

We hypothesized that it would be feasible to visualize the adrenal arteries and measure their blood flow velocities by Doppler with equipment that can be incorporated into a clinical setting. Toward this end, we decided to perform an exploratory ultrasound study on the arterial supply of the adrenal glands in human fetuses in the second and third trimesters.

The aim of this exploratory study was to develop a systematic approach for measuring arterial flow velocities to the adrenal glands in human fetuses in the second and third trimesters. Our main objectives were to define the three main arteries that supply the adrenal gland, describe their course and origin, and report the rate of obtaining Doppler velocity measurements for each of the arteries.

Key message

This study shows the inferior adrenal artery to have the highest detection rate of the fetal adrenal arteries. A technique to visualize and perform Doppler velocimetric measurement on this artery is described in detail.

2 | MATERIAL AND METHODS

This was a prospective cross-sectional study where we recruited women with singleton pregnancies who presented for their routine second-trimester ultrasound screening at the maternal-fetal medicine outpatient clinic at our hospital. The participants were assigned to one ultrasound examination each. We planned to enroll 75 participants as we estimated this number to be sufficient. All pregnancies were dated based on second-trimester ultrasound biometry.

The exclusion criteria were: A history of diabetes mellitus, coagulopathies, rheumatic disease, chronic hypertensive disorders, previous placental abruption, previous intrauterine fetal demise, previous delivery earlier than gestational week 37, previous or current hypertensive disorders of pregnancy (throughout the pregnancy), previous or current FGR, previous or current gestational diabetes (throughout the pregnancy), previous bariatric surgery or diagnosed fetal anomalies.

We primarily used a GE Voluson E10 2019 with a C2-9 probe and Slowflow software (GE Healthcare, Zipf, Austria). Some examinations were done using a Philips Epiq Elite with a V9-2 probe and Microflow Imaging software (Philips Medical Systems International B.V., Best, The Netherlands). Examinations were performed by two of the authors. A number of participants were examined by both operators to assess the interobserver variability. The examinations were limited to one hour, and we aimed to keep the thermal index for bone (TIB) at 1.0 or below at all times. The following background parameters were recorded at the time of the examination: Medical history, maternal height and prepregnant weight, self-reported ethnicity, parity, maternal age, and gestational age at the time of the examination.

We aimed to visualize the blood flow and measure its velocities in the three main vessels supplying each adrenal gland: The inferior adrenal artery, the middle adrenal artery, and the inferior phrenic artery. The velocities measured were the peak systolic velocity (PSV), end-diastolic velocity (EDV), and time-averaged maximum velocity (TAMAX). The pulsatility index (PI) was calculated as $\frac{PSV - EDV}{TAMAX}$.[24] We aligned the Doppler beam with the artery with the intention of keeping the angle of interrogation below 30 degrees.

The protocol was approved on November 28, 2018 by the South-Eastern Norway Regional Committee for Medical and Health Research Ethics (2018/1923/REK sør-øst) in line with the revised Helsinki declaration.[25]

2.1 | Statistical analyses

IBM SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used for all descriptive statistics, which are presented as counts and percentages for categorical variables and as mean, standard deviations (SD), and full ranges for continuous variables. Inter-observer reliability for the measurement of PI was estimated using the intraclass correlation coefficient (ICC) assessing the degree of absolute agreement between individual measurements in a two-way random effects model. The ICC is presented with a 95% confidence interval (CI). Limits of Agreement (LoA) for the PI measured in the right vs. the left artery were estimated using the Bland–Altman method.[26] These are the limits within which 95% of differences between the PI measured in the right vs the left artery are expected to lie. ICC and LoA were assessed in Stata v. 17.0 (USA), using functions icc and blandaltman.[27]

3 | RESULTS

We included 75 women in our study period. Three of the primarily recruited participants were later excluded due to hypertension (two participants) and gestational diabetes (one) in the current pregnancy. Thus, a total of 72 participants entered the final analysis. Characteristics of the participants, examinations, and deliveries are presented in Table 1.

Of a total of 72 examinations, two were carried out using the Philips scanner, and 70 with the GE Voluson. Author 1 (ØB) performed 50 examinations, Author 2 (RKS) seven, and 15 fetuses were assessed by both operators. For the interobserver variability study, seven fetuses were scanned by both examiners separately. The analysis yielded an ICC of 0.62 with a 95% CI (−0.04 to 0.92). All examinations were kept below 60 minutes; TIB briefly exceeded 1.0 in 21 examinations (29%).

We assessed the arterial supply to the adrenal glands in two planes: An oblique coronary plane including the aorta, the renal artery, the cranial part of the kidney and the adrenal gland (Figure 1), and an oblique transversal plane at the level of the cranial part of the kidney, including the aorta and the renal artery in the frame (Figure 2). We found anatomical variation in the arterial blood supply to the adrenal glands, both in numbers, origin, and their course across the gland.

In all participants, we found at least one vessel originating from the aorta or the renal artery running between the lower part of the gland and area around the upper pole of the kidney (Figure 1). We defined this as the inferior adrenal artery and found this to be the most prominent vessel supplying the gland. The course of the vessel, when seen in the oblique coronary view, had a steep curve running from the area where the ipsilateral renal artery entered the kidney and continued toward the upper renal pole. From here it curved caudally toward the lateral side of the kidney.

TABLE 1 Clinical and demographic characteristics of the participants ($n=72$).

	Number (%)	Mean ± SD	Range
Maternal ethnicity: Norwegian	58 (81)		
Fetal sex: female	36 (50)		
Maternal age (y)		30.7 ± 4.6	22–41
Body Mass Index (kg/cm^2)		21.8 ± 2.4	16.8–28.4
Parity			0–3
0	26 (36)		
1	34 (47)		
> 1	12 (17)		
Gestational age (weeks)		24.9 ± 3.9	18.1–37.9
Mode of delivery: Spontaneous	59 (82)		
Mode of delivery: Cesarean section	7 (10)		
Gestational age at birth (weeks)		40.3 ± 1.2	36.7–42.1
Birth weight (g)		3659 ± 477	2254–4650
5 min Apgar			6–10
10	58 (81)		
7–9	13 (18)		
< 7	1 (1)		

Abbreviation: SD, Standard deviation.

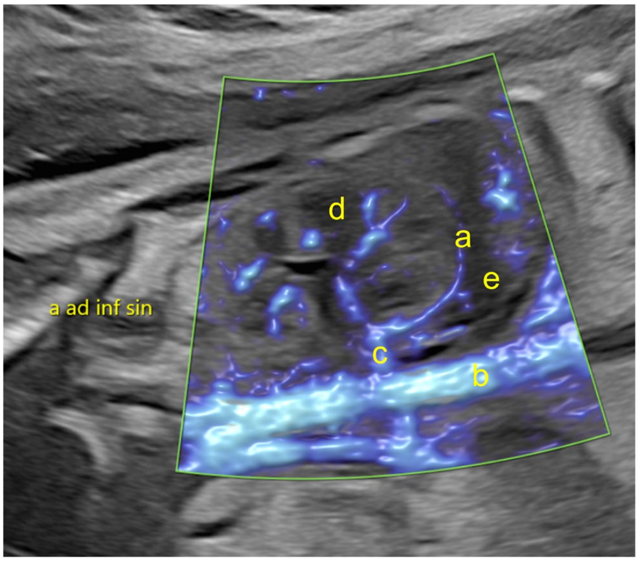

FIGURE 1 The fetal left inferior adrenal artery is visualized originating from the renal artery and curving over the convex cranial surface of the kidney in a 26 weeks fetus in a participant with a BMI of 19.2. a = Left inferior adrenal artery; b = Aorta; c = Left renal artery; d = Left fetal kidney; e = Left fetal adrenal gland.

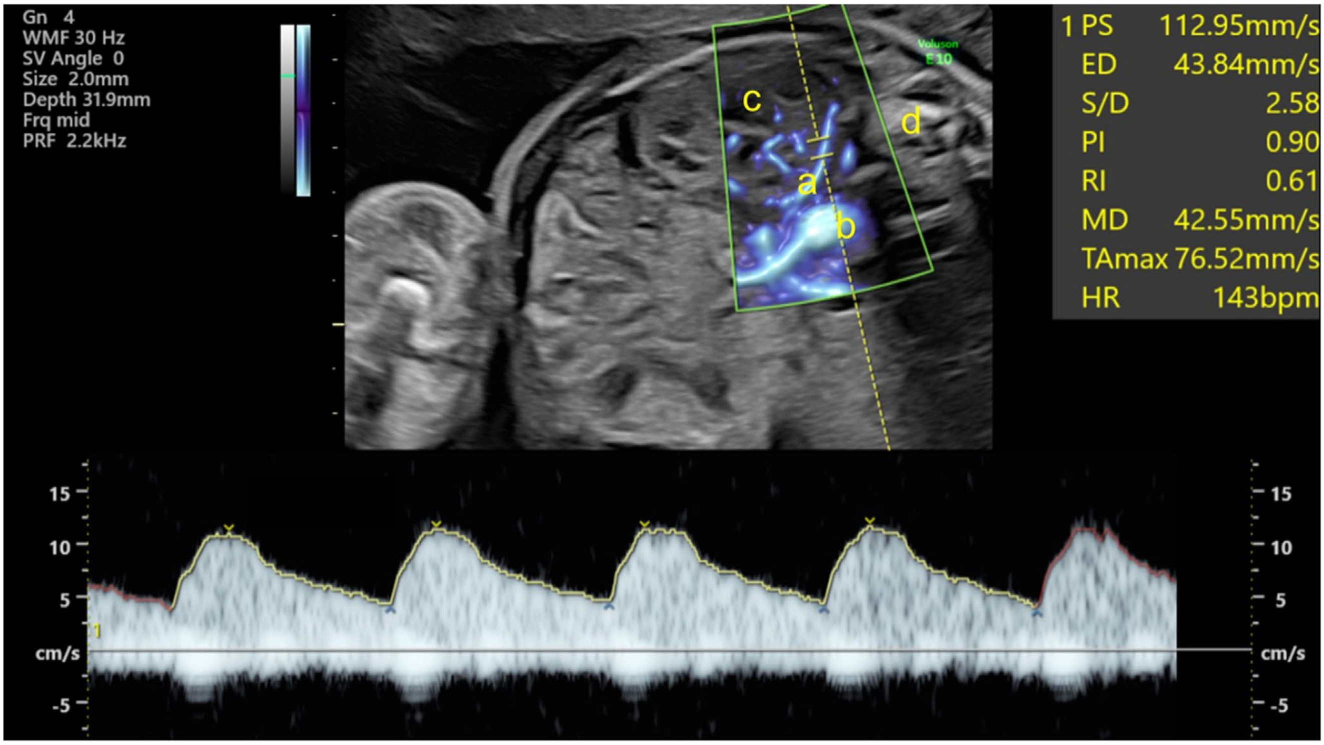

FIGURE 2 Pulsed Doppler waveforms of the left inferior adrenal artery (lower panel) in a 24 weeks fetus in a participant with a BMI of 22.3. The panel in the upper left corner shows two-thirds of the fetal abdomen in a transverse view with the left abdominal side facing upwards. The spine is facing toward the upper right corner of the upper panel. a = Left inferior adrenal artery; b = Aorta; c = Left fetal kidney; d = Fetal spine.

TABLE 2 Number of fetuses in which we were able to obtain a measure of pulsatility index (PI) in the six vessels interrogated, with PI characteristics ($n = 72$).

Vessel	Number (%)	PI mean ± SD	PI range
Inferior adrenal arteries			
Right	45 (63%)	1.06 ± 0.11	0.77–1.35
Left	44 (61%)	1.06 ± 0.11	0.83–1.23
Any	66 (92%)		
Middle adrenal arteries			
Right	8 (11%)	0.99 ± 0.12	0.85–1.16
Left	7 (10%)	0.96 ± 0.16	0.75–1.19
Any	15 (21%)		
Inferior phrenic arteries			
Right	16 (24%)	1.09 ± 0.11	0.94–1.33
Left	19 (26%)	1.06 ± 0.09	0.92–1.24
Any	28 (39%)		

Abbreviations: PI, pulsatility index; SD, standard deviation.

We succeeded in measuring blood flow velocities in the inferior adrenal artery in 66 (92%) of the 72 participants (Tables 2 and S1). In some cases, there were two or more arteries running along the inferior surface of the gland. To maintain a uniform and reproducible technique, we measured the most dorsal of these vessels, as seen in a transverse view, which resembled more closely the course found in fetuses with a single artery supplying the inferior parts of the gland.

We measured the blood flow velocities by Doppler ultrasound in the oblique coronary view where the artery curved along the upper pole of the kidney. The oblique coronary view was used as default. In some cases, the course of the artery or fetal position favored the transverse view. In the transverse view, we measured the blood flow velocities at the middle third of the artery, as this best corresponded with the chosen sample site in the oblique coronary view (Figure 2). Flowcharts for suggested stepwise instruction on how to locate and measure the inferior adrenal artery flow velocity in both an oblique coronary view and a transverse view are presented in Figures S1 and S2.

The inferior phrenic artery was the second most commonly measured vessel. It was successfully measured in 28 (39%) of the 72 participants (Tables 2 and S1). This vessel was also visualized for Doppler measurements in both the oblique coronary view described above, and a transverse view including the caudal parts of the diaphragm but not the kidney. The artery branched off from the aorta or the coeliac trunk and ran along the inferior surface of the diaphragm, over the upper surface of the adrenal gland (Figure S3). Blood flow velocities were measured close to its origin at the aorta or coeliac trunk, where the curve along the inferior margin of the diaphragm allowed for the lowest insonation angle.

We considered any arteries with a course between the upper kidney pole and the top of the adrenal gland to be middle adrenal arteries. They originated from the aorta, the ipsilateral renal artery or the ipsilateral inferior adrenal artery. We managed to measure the middle adrenal artery in 15 (21%) of the 72 participants (Table 2 and Table S1).

The PI in the vessels supplying the adrenal gland was generally low, indicating low vascular impedance, and similar between the vessels (Table 2). Comparing PI in the right vs the left inferior adrenal arteries ($n=23$), we found a mean difference of −0.001 units (SD, 0.105), with 95% LoA given by (−0.207, 0.205). Figure S4 displays the corresponding Bland–Altman plot.

4 | DISCUSSION

This study has shown that it is possible to visualize the fetal adrenal arteries in a large majority of a low-risk population using modern ultrasound equipment and measure blood flow velocities using pulsed wave Doppler. Three adrenal arteries have been defined based on their area of contact with the gland. Furthermore, we have developed a technique for measuring blood flow velocities in these arteries using a systematic visualization approach to minimize the problem of anatomical variation in assessing blood supply of the adrenal glands. The highest success rate was achieved for the inferior adrenal artery. Visually we found this to be the largest single artery supplying the gland, and we consider it the prime candidate for further study, based on its prominence, predictable presence, and course.

Several studies have sought to establish reference ranges for the PI of human fetal adrenal arteries,[11–13,28,29] and measured PI in growth-restricted fetuses,[30] but have not addressed the issues of anatomical variation of adrenal arterial vasculature in human fetuses. One study has described measuring an artery positioned inside the adrenal gland,[13] but we have found no anatomical study that supports the presence of arteries inside the gland.[31] None of the aforementioned studies have described the method of locating the vessel in sufficient detail to enable replication. One study has defined the inferior adrenal artery with both origin and final course as obligate parameters.[28] The anatomical variance implies that in a significant number of fetuses no artery can be found fulfilling both these criteria; we have limited our definition to the final course of the vessel. The PI of the inferior adrenal artery in our study is within the range described in the latest and largest study of human fetal adrenal blood supply.[28] We found no systematic differences in PI between the left and the right inferior adrenal artery, but due to the limited sample size, the results of this analysis must be interpreted with caution.

At the start of our data collection, we visualized the inferior adrenal artery only in the oblique coronary view described earlier. However, after acknowledging the anatomical variations both in the numbers of vessels and their course, we found that adding the transverse view secured the measurements were performed as uniformly as possible. Omitting the transverse view risks overlooking a second inferior adrenal artery. Studies have found that the inferior adrenal artery supplied the renal surface of the adrenal gland and the lower part of its anterior and posterior surface, most commonly running on the dorsal side of the kidney.[19,22] The addition of the transverse view enables the examiner to consistently measure the correct vessel in serial measurements over several days or weeks, for instance when monitoring a growth-restricted fetus. The oblique coronary view is needed to identify the inferior adrenal artery running between the kidney and the adrenal gland. Omitting this view increases the risk of not visualizing the inferior adrenal artery, but rather erroneously finding the middle adrenal artery, the inferior phrenic artery, or another vessel entirely. The risk of assessing the wrong artery increases if the visualization is poor or the fetal lie is unfavorable. Both views are therefore crucial in obtaining reproducible and reliable measurements of the correct vessel. We have found no other study seeking to assess the fetal adrenal arteries that have moved beyond using the transverse view.[11–13,28,30]

The main aim of this study was not to establish reference values but to develop a systematic approach for the measurement of arterial flow velocities in the fetal adrenal arteries, which was considered to need the present number of participants. Thus, PI values obtained in the present exploratory study should be interpreted with caution. A study with a longitudinal design and higher power is needed to describe the development of the PI during pregnancy.

The technique was repeatedly refined during the study, and results obtained in the early period may have been more prone to errors than in the later. The low body mass index (BMI) of our study population was favorable for our success rate, but we were able to measure the PI of the inferior adrenal artery also in the three participants with the highest BMI. However, it is probable that a higher BMI would have made the visualization of the vessels more challenging.

We find the difficulty of visualizing the inferior adrenal artery and performing blood velocimetric measurements comparable to the same procedures for the ductus venosus. In our study, most examinations were performed by a doctor in his obstetrical and gynecological training (ØB). We do not believe the procedure to be too complicated for clinical implementation.

Our rather modest sample size also means there could exist anatomical variations beyond those described here. The inferior adrenal artery is known to vary substantially at the origin of the vessel, and one review article found it to vary between geographical regions although statistical analyses were not reported.[20] Some anatomical studies also report considerable variation in the course of the vessels, but we have not found any studies that have explored whether variations between different regions or populations exist.[14,17,19] There is considerable evidence that such geographical variation does exist in other vascular sections, such as the circle of Willis.[32] Although we observed an artery meeting our criteria for the inferior adrenal artery in all our participants, it does not exclude other variations in other populations.

No serious consistent adverse effects of prenatal ultrasound have been demonstrated in human fetuses.[33] Nonetheless, it is prudent to keep ultrasound exposure to the lowest intensity needed to obtain reliable information, in particular when using Doppler ultrasound.[34] The TIB was monitored throughout the examinations and immediately reduced when exceeding 1.0, ensuring the lowest exposure level compatible with obtaining the relevant information.

Having established a systematic technique for the Doppler assessment of arterial blood flow velocity to the human fetal adrenal glands, we believe the next step should be to establish a longitudinal reference range for the PI of the inferior adrenal artery and ultimately test this measurement in the detection and surveillance of FGR.

5 | CONCLUSION

We have developed and described a technique that makes it possible to visualize and measure flow velocity in the human fetal adrenal arterial blood supply with a high success rate.

AUTHOR CONTRIBUTIONS

Øystein Bergøy: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, visualization, writing—original draft, and reviewing and editing. Torvid Kiserud, Jørg Kessler, and Kristine Moi Økland: conceptualization, methodology, supervision, writing—reviewing and editing. Ingvild Dalen: data curation, formal analysis, methodology, visualization, writing—reviewing and editing. Ragnar Kvie Sande: conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, project administration, visualization, and writing—reviewing and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ETHICS STATEMENT

The protocol of this study was approved on November 28, 2018 by the South-Eastern Norway Regional Committee for Medical and Health Research Ethics (reference number 2018/1923/REK sør-øst.). Written informed consent was obtained from all participants. The first participant enrolled on April 12, 2019.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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