The Relationship between the Fetal Volume-Corrected Renal Artery Pulsatility Index and Amniotic Fluid Volume

FDT491749 - Fetal Diagn Ther - ISSN 1015–3837 (for internal use only)							
Code 3	PE	CE	Copy edited	Figures	Tables	Suppl. mat.	Typesetting
FDT	zm	cg	25.9.18	2	3		mü
Language	E	Second Language		Third Language		Template_Art	ZU

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Article title	The Relationship between the Fetal Volume-Corrected Renal Artery Pulsatility Index and Amniotic Fluid Volume
Article title second language	
Article title third language	
Subtitle	
Short title	Renal Artery PI and Amniotic Fluid
Section title	Original Paper

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Citation line	Journal			
	Fetal Diagn Ther			
10.1159/000491749	Article-Nr	491749	CCCode	
ISSN	1015–3837			
ISBN				

Received	Received: January 10, 2018
Accepted	Accepted after revision: July 2, 2018
Revised	
Published online	Published online: ■■■

Keywords	Keywords
	Renal artery Amniotic fluid Oligohydramnios Doppler ultrasound Fetal kidney

Keywords Second Language	

Keywords Third Language	

Abbreviations	

Abstract	Abstract

Introduction: To evaluate if the volume-corrected renal artery pulsatility index (vcRA-PI) is more closely related to the amniotic fluid level than the uncorrected or the gestational age (GA)-adjusted RA-PI. **Methods:** RA-PI and kidney volume were measured in low- and high-risk pregnancies at 17–38 weeks. Fetal anomalies associated with nonrenal causes of abnormal amniotic fluid volume were excluded. The vcRA-PI was calculated by dividing the RA-PI by the renal volume. The RA-PI was adjusted for GA, to obtain the GA-adjusted RA-PI. The uncorrected, GA-adjusted, and the vcRA-PI were related to the amniotic fluid level using nonparametric tests and receiver operating characteristic (ROC) curve analyses. **Results:** 146 examinations from 59 pregnancies were reviewed. Of these, 16 had oligo- and 15 had polyhydramnios. A higher vcRA-PI was associated with oligohydramnios (OR 2.54, 95% CI 1.67–3.86, $p < 0.001$), while the uncorrected RA-PI and GA-adjusted RA-PI were not able to predict oligohydramnios. ROC curve analysis showed a high predictive accuracy of the vcRA-PI for oligohydramnios (AUC 0.84, 95% CI 0.72–0.94). On the other hand, the uncorrected RA-PI and GA-adjusted RA-PI significantly predicted polyhydramnios ($p = 0.04$ and 0.02, respectively), while the vcRA-PI did not. **Conclusion:** The vcRA-PI is superior to the uncorrected and the GA-adjusted RA-PI in predicting oligohydramnios.

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Introduction

In fetal conditions where information on renal function is important, the amount of amniotic fluid measured by ultrasound is used as a marker of fetal urine production and therefore kidney function. However, the reliability of the ultrasound measurement of amniotic fluid in reflecting renal function is limited. First, none of the ultrasound techniques to measure the amniotic fluid correlate closely with the actual amniotic fluid volume [1, 2], and second, changes in amniotic fluid level can be the result of different mechanisms other than changes in fetal urine production. Examples include obstruction of the fetal gastrointestinal tract leading to impaired fetal swallowing and polyhydramnios, or complete lower urinary obstruction (LUTO) leading to oligo/anhydramnios.

Since renal filtration and urine production depend on arterial perfusion of the organ, renal artery Doppler velocimetric parameters could potentially be a better indirect marker of fetal kidney function. Based on this assumption, some studies have evaluated the association of fetal renal artery pulsatility index (RA-PI) with amniotic fluid level [3–8]. However, they have yielded conflicting results, showing no consistent significant relationship throughout gestation [3, 4]. A possible explanation is that in none of these studies were the renal artery resistance indices corrected for the organ volume. Downstream vasculature resistance is affected by the size of the vascular bed and therefore the size of the organ. For that reason, we conducted a study to see if volume-corrected RA-PI (vcRA-PI) is more closely related to the level of amniotic fluid than the uncorrected or the gestational age (GA)-adjusted RA-PI.

Material and Methods

This is a retrospective study on pregnant women receiving obstetric ultrasound at the Johns Hopkins Center for Fetal Therapy between June 2015 and January 2017. The study protocol was approved by the Institutional Review Board and patients gave informed consent to participate. Low- and high-risk pregnancies at 17–38 weeks during which ultrasound Doppler assessment of the fetal renal artery waveform was performed were included. At the Johns Hopkins Center for Fetal Therapy, renal size and Doppler of the renal vessels are assessed in all pregnancies, when technically feasible. Once the cases were identified, each study was reviewed. Pregnancies complicated by rupture of membranes were excluded. Fetal anomalies associated with nonrenal causes of abnormal amniotic fluid level, such as fetal chest mass, congenital diaphragmatic hernia, duodenal atresia, complete LUTO, and urinary tract dilation likely due to ureteropelvic or ureterovesical junction obstruction and vesicoureteral reflux, were also excluded. Partial LUTO without megacystis was included in the analysis, as the absence of bladder distension likely suggested passage of urine through the urethra secondary to resolved/ partial obstruction at the time of the examination.

All cases underwent a standardized ultrasound and fetal Doppler evaluation using high-frequency, high-resolution probes (Voluson Expert 8 or 10, General Electric, GE Healthcare Technologies, WI, USA). Some pregnancies had repeat examinations throughout gestation, and these were also included in the analysis. All recordings were performed by the same two operators. First, amniotic fluid volume was measured. Oligohydramnios was defined as an amniotic fluid index of less than 5 cm, or a maximum vertical pocket of less than 2 cm. Polyhydramnios was defined as an amniotic fluid index of more than 25 cm, or a maximum vertical pocket of more than 8 cm. Then, on a coronal view of the fetal abdomen, the renal arteries were identified emerging from the aorta, using color flow mapping. Pulsed Doppler was applied at the proximal third of the renal arteries, using a 1- to 2-mm gate size, with an angle of insonation as close as possible to 0° (Fig. 1) [5, 9]. Both the right and left renal artery Doppler waveforms were obtained, when technically possible, in the absence of fetal breathing, and RA-PI was recorded. When renal size was measured by two-dimensional (2D) ultrasound, three orthogonal kidney diameters were applied to the volume formula of an ellipsoid shape to obtain a volume estimate (length × transverse × antero-posterior × 0.523) [10].

The vcRA-PI was calculated by dividing the left and right RA-PI by the ipsilateral renal volume, when available, for each fetus. The RA-PI was then adjusted for GA, using published reference ranges, to obtain *z*-score values [5]. For each of the 3 parameters (uncorrected RA-PI, vcRA-PI, and GA-adjusted RA-PI), the average between the right and left side was used, when both sides were recorded. A logistic regression analysis was used to assess the association between each of the renal flow parameters studied and the level of amniotic fluid (oligo- or polyhydramnios), and the odds ratios were calculated. We used a generalized estimating equation model to take into account the fact that some patients in our cohort had repeat examinations throughout gestation. Then, for the parameters that were found to be significantly associated with oligohydramnios, a receiver operating characteristic (ROC) curve analysis was performed to estimate covariates' predictive ability for oligohydramnios. Statistical analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant. Finally, for each parameter studied, a post hoc power analysis was performed using G-Power 3.0 to assess the statistical power of our analysis.

Results

One hundred and forty-six examinations from 59 pregnancies met the inclusion criteria (33 singleton and 26 multiple pregnancies). Fourteen pregnancies were low-risk, the other 45 were considered high-risk. This group included fetuses with anomalies other than those described among the exclusion criteria, as well as normal or complicated dichorionic and monochorionic diamniotic pregnancies. Median GA at the examination was 27.7 weeks (IQR 23.1–32.3). Some patients had repeat examinations throughout gestation (average number of examinations per pregnancy was 2). Of the 146 examinations, 115 (79%) showed normal amniotic fluid level, 16 (11%) had oligohydramnios, and 15 (10%) had polyhydramnios. Characteristics of the cases with an abnormal amniotic fluid level are reported in Table 1.

The uncorrected and the GA-adjusted RA-PI were available in all cases. The vcRA-PI was available in 108 of 146 examinations. Tables 2 and 3 show the distribution of the PI values across groups of normal and abnormal amniotic fluid level. A higher vcRA-PI was associated with oligohydramnios (OR 2.54, 95% CI 1.67–3.86, $p < 0.001$), while the uncorrected RA-PI and GA-adjusted RA-PI were not found to be significant predictors of oligohydramnios (Table 2). On the other hand, the uncorrected RA-PI and GA-adjusted RA-PI significantly predicted polyhydramnios ($p = 0.04$ and 0.02, respectively), while the vcRA-PI did not (Table 3).

The ROC curve analysis showed high predictive accuracy of the vcRA-PI for oligohydramnios (AUC 0.84, 95% CI 0.72–0.94) (Fig. 2). The value of vcRA-PI with the best trade-off of sensitivity and specificity was 0.73, with a sensitivity of 83% and a specificity of 71% for oligohydramnios.

A post hoc power analysis showed a power of 92% for the analysis of the relation between vcRA-PI and oligohydramnios. For the analysis of the uncorrected RA-PI and GA-corrected RA-PI, the power was less than 50%.

Discussion

The identification of a good marker of fetal kidney function will facilitate the diagnosis and follow-up of fetal pathological conditions that affect fetal kidneys. In this study, we evaluated if correction for renal volume increases the ability of the RA-PI to predict abnormal level of amniotic fluid, which reflects changes in fetal urination. Our results showed that the vcRA-PI is superior to the uncorrected and the GA-adjusted RA-PI in predicting oligohydramnios. The etiology of oligohydramnios remains heterogeneous. By excluding cases with complete LUTO leading to oligo/anhydramnios, as well as those with ruptured membranes, we aimed to study only those conditions in which the reduction of amniotic fluid was related to reduced fetal urine production, and therefore impaired kidney function.

Previous studies that have evaluated the association of fetal RA-PI with amniotic fluid level have yielded conflicting results [3–6]. In a longitudinal study of 63 low-risk pregnancies followed from 16 to 41 weeks, no correlation was found between the amniotic fluid index and the uncorrected fetal RA Doppler velocimetric parameters at any gestational age [4]. In two small studies on growth-restricted fetuses [11] and post-term pregnancies [7], respectively, the uncorrected RA resistance index values studied did not correlate with amniotic fluid level. These reports are consistent with our finding that the uncorrected RA-PI does not predict oligohydramnios. In another longitudinal study, the RA-PI was evaluated in low-risk patients at three different GAs, and it was found to be significantly different between cases with oligohydramnios and controls at 28 weeks, but not at 22 or 34 weeks [3].

Different results were observed in a study on 10 post-term fetuses with oligohydramnios that were found to have a significantly higher RA-PI compared to controls with normal amniotic fluid level [8]. Similar findings were reported by Yoshimura et al. [6] at 36–40 weeks, in normal and growth-restricted fetuses. In the study by Mari et al. [5], the RA-PI in twin pregnancies with polyhydramnios was significantly lower that the PI in those with oligohydramnios. However, the authors did not compare the PI of fetuses with oligohydramnios to those with normal amniotic fluid.

While comparison between different studies is difficult due to heterogeneous inclusion and exclusion criteria, a possible explanation of the inconsistent results, in view of our findings, is that the RA-PI was never adjusted for renal size. The significant relationship between a higher vcRA-PI and the development of oligohydramnios, and the inability of the uncorrected or GA-adjusted RA-PI to predict oligohydramnios in the present study suggest that such correction is advisable, in order to use RA blood flow parameters as a marker of fetal kidney function.

Physiologically, it is known that renal urine production depends on renal plasma flow, which is a function of kidney perfusion, and that vascular modifications play a major role in the decreased urine output. The vcRA-PI could potentially be used to indirectly evaluate deterioration of renal function in early stages, thus becoming a useful tool for the follow-up of pregnancies where information on renal function is important. The accuracy of such a parameter may be higher than the measurement of amniotic fluid level, which can vary in response to different mechanisms other than renal urine production (e.g., mechanical obstruction of the lower urinary tract), and better than the uncorrected or the GA-adjusted RA-PI, which does not take into account the size of the kidney. Another method that has been suggested to estimate fetal urine output consists of calculating the change in bladder volume over a period of time [12]. However, the assessment of bladder size and filling is often impractical, because it requires long observation times.

On the other hand, urine production is also determined by tubular reabsorption capability, which is not reflected by RA flow waveform parameters, and it is not possible to determine how much this effect can impact the relationship between RA-PI and renal function. Further studies are necessary to investigate the efficacy of renal blood flow assessment in the prediction of renal function, by comparing renal blood flow with fetal urinary electrolytes, when available.

The reason why the vcRA-PI did not predict polyhydramnios in our study may be that when the induced vasodilation of the renal arteries reaches its maximum and is not going to change anymore, it is not possible to demonstrate a consistent relationship of vcRA-PI with the increased level of amniotic fluid. Moreover, it is clinically more relevant to have a good parameter to assess renal function in the setting of oligohydramnios, where the cause and the degree of reduced fetal urination may be uncertain, than to study renal Doppler flow in fetuses with polyhydramnios, where other signs are often present to guide the diagnosis.

The current study had some limitations. We did not assess renal venous blood flow. Additional information on the vascular field could be achieved by considering not only the feeding vessel, but also the draining vessel. In our study the intraobserver reproducibility of kidney measurements was not tested. However, standard 2D measurements of the fetal kidneys is the earliest and simplest method utilized to assess renal size at different GAs, and it has been used to build normal fetal kidney nomograms. Moreover, the reproducibility of 2D fetal renal volumes is considered superior to the 3D volumes, for which good reproducibility has not yet been demonstrated [13].

Finally, while we found that the vcRA-PI is a good predictor of oligohydramnios, with a test power of 92%, we acknowledge that our study may be underpowered to detect a significant relationship between oligohydramnios and the uncorrected or GA-corrected RA-PI. However, our results suggest that the vcRA-PI performs better than the other two parameters.

Strengths of this study include the description of a novel index that has not been investigated for its relationship with amniotic fluid level in previous studies, and the inclusion of both normal and complicated pregnancies, in particular complicated monochorionic twins, a subgroup that is subject to changes in amniotic fluid volume secondary to changes in urine production.

In conclusion, the vcRA-PI is superior to the uncorrected and the GA-adjusted RA-PI in predicting oligohydramnios. Further studies are needed to investigate the association of vcRA-PI with fetal urinary electrolyte levels and postnatal renal function.

Disclosure Statement

The authors declare no conflict of interest.

References

1 Magann EF, Chauhan SP, Whitworth NS, Klausen JH, Saltzman AK, Morrison JC. Do multiple measurements employing different ultrasonic techniques improve the accuracy of amniotic fluid volume assessment? Aust N Z J Obstet Gynaecol. 1998 May;38(2):172–5.

2 Magann EF, Nolan TE, Hess LW, Martin RW, Whitworth NS, Morrison JC. Measurement of amniotic fluid volume: accuracy of ultrasonography techniques. Am J Obstet Gynecol. 1992 Dec;167(6):1533–7.

3 Benzer N, Pekin AT, Yılmaz SA, Kerimoğlu OS, Doğan NU, Çelik Ç. Predictive value of second and third trimester fetal renal artery Doppler indices in idiopathic oligohydramnios and polyhydramnios in low-risk pregnancies: a longitudinal study. J Obstet Gynaecol Res. 2015 Apr;41(4):523–8.

4 Figueira CO, Surita FG, Dertkigil MS, Pereira SL, Bennini JR Jr, Morais SS, et al. Longitudinal reference intervals for Doppler velocimetric parameters of the fetal renal artery correlated with amniotic fluid index among low-risk pregnancies. Int J Gynaecol Obstet. 2015 Oct;131(1):45–8.

5 Mari G, Kirshon B, Abuhamad A. Fetal renal artery flow velocity waveforms in normal pregnancies and pregnancies complicated by polyhydramnios and oligohydramnios. Obstet Gynecol. 1993 Apr;81(4):560–4.

6 Yoshimura S, Masuzaki H, Gotoh H, Ishimaru T. Fetal redistribution of blood flow and amniotic fluid volume in growth-retarded fetuses. Early Hum Dev. 1997 Feb;47(3):297–304.

7 Bar-Hava I, Divon MY, Sardo M, Barnhard Y. Is oligohydramnios in postterm pregnancy associated with redistribution of fetal blood flow? Am J Obstet Gynecol. 1995 Aug;173(2): 519–22.

8 Selam B, Koksal R, Ozcan T. Fetal arterial and venous Doppler parameters in the interpretation of oligohydramnios in postterm pregnancies. Ultrasound Obstet Gynecol. 2000 May;15(5):403–6.

9 Haugen G, Godfrey K, Crozier S, Hanson M. Doppler blood flow velocity waveforms in the fetal renal arteries: variability at proximal and distal sites in the right and left arteries. Ultrasound Obstet Gynecol. 2004 Jun;23(6):590–3.

10 Hricak H, Lieto RP. Sonographic determination of renal volume. Radiology. 1983 Jul; 148(1):311–2.

11 Stigter RH, Mulder EJ, Bruinse HW, Visser GH. Doppler studies on the fetal renal artery

in the severely growth-restricted fetus. Ultrasound Obstet Gynecol. 2001 Aug;18(2):141–5.

12 Campbell S, Wladimiroff JW, Dewhurst CJ. The antenatal measurement of fetal urine production. J Obstet Gynaecol Br Commonw. 1973 Aug;80(8):680–6.

13 Brennan S, Watson D, Rudd D, Schneider M, Kandasamy Y. Evaluation of fetal kidney growth using ultrasound: A systematic review. Eur J Radiol. 2017 Nov;96:55–64.

Appendix after References (Editorial Comments)

Legend(s)

Fig. 1. Doppler flow velocity waveform obtained from the right renal artery using a coronal view of the fetal abdomen, with color Doppler. Pulsed Doppler is applied at the proximal third of the renal arteries, using a 1- to 2-mm gate size, with an angle of insonation as close as possible to 0°.

Fig. 2. Receiver operating characteristic curve of vcRA-PI for oligohydramnios (AUC 0.84, 95% CI 0.72–0.94).

Table(s)

Footnote(s)

Table 1. Characteristics of the cases with abnormal amniotic fluid level

Amniotic fluid anomaly	Type of anomaly	Pregnancies, *n*	Exams, *n*
Oligohydramnios (*n* = 16)	IUGR singleton	1	1
	sIUGR (MC twin)	1	1
	TTTS donor (pre-laser)	1	1
	TTTS + sIUGR donor (pre-laser)	3	3
	TTTS donor (post-laser)	2	3
	Hypoplastic left heart syndrome	1	2
	Partial LUTO[a]	1	3
	Renal failure secondary to medication exposure	1	2
Polyhydramnios (*n* = 15)	MC-DA twins with discordant fluid (recipient)	4	10
	TTTS recipient (stage 5)	1	2
	TTTS recipient (post-laser)	2	3

IUGR, intrauterine growth restriction; sIUGR, selective intrauterine growth restriction; MC, monochorionic; DA, diamniotic; TTTS, twin-to-twin transfusion syndrome; LUTO, lower urinary tract obstruction. [a] Without megacystis at the time of the exam.

Table 2. Association between renal artery PI parameters and oligohydramnios

Parameter	Normal AF (*n* = 115)	Oligohydramnios (*n* = 16)	OR (95% CI)[a]	*p*
Uncorrected RA-PI	2.46 (2.18 to 2.76)	2.47 (2.15 to 3.25)	1.52 (0.77–3.01)	0.23
GA-adjusted RA-PI *z*-score	–0.34 (–1.2 to 0.26)	–0.99 (–1.78 to 1.2)	1.01 (0.73–1.41)	0.94
vcRA-PI[b]	0.49 (0.30 to 0.82)	1.30 (0.80 to 3.72)	2.54 (1.67–3.86)	<0.001

Data are given as median (25th to 75th IQR) unless indicated otherwise. AF, amniotic fluid; RA, renal artery; PI, pulsatility index; GA, gestational age; vc, volume corrected. [a] Normal amniotic fluid used as reference category. [b] Available in 108 of 146 cases.

Table 3. Association between renal artery PI parameters and polyhydramnios

Parameter	Normal AF (*n* = 115)	Polyhydramnios (*n* = 15)	OR (95% CI)[a]	*p*
Uncorrected RA-PI	2.46 (2.18 to 2.76)	2.20 (1.89 to 2.48)	0.18 (0.04–0.74)	0.02
GA-adjusted RA-PI *z*-score	–0.34 (–1.2 to 0.26)	–1.18 (–2.1 to –0.47)	0.55 (0.32–0.96)	0.04
vc-RA-PI[b]	0.49 (0.30 to 0.82)	0.50 (0.32 to 0.93)	0.64 (1.53–2.67)	0.54

Data are given as median (25th to 75th IQR) unless indicated otherwise. AF, amniotic fluid; RA, renal artery; PI, pulsatility index; GA, gestational age; vc, volume corrected. [a] Normal amniotic fluid used as reference category. [b] Available in 108 of 146 cases.

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