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Measurement of fetal urine production to differentiate causes of increased amniotic fluid volume

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KEYWORDS: 3D ultrasonography; fetal bladder volume measurement; fetal urine production rate; polyhydramnios; VOCAL

ABSTRACT

Objectives *In polyhydramnios, amniotic fluid (AF) volume can be increased not only as a result of increased fetal urine production, but also due to several other factors, including impairment of both fetal swallowing and gastrointestinal (GI) absorption of AF. Our aim was to evaluate whether measurement of the fetal urine production rate (UPR) can be used to differentiate the causes of increased AF volume.*

Methods *This cross-sectional study included 54 pregnant women with an increased amniotic fluid index (AFI), defined as AFI ≥ 18 cm, divided into two groups according to the presence of fetal anomalies that are associated with impairment of fetal swallowing or decreased GI absorption of AF (Group 1, n = 14) or the absence of fetal anomalies (Group 2, n = 40). The control group included 96 normal pregnancies with normal AFI (8 ≤ AFI < 18 cm) (Group 3). Fetal UPR was obtained by serial bladder volume measurements (two to four times, with a median interval of 5 min between each) using the rotational method of Virtual Organ Computer-aided AnaLysis (VOCAL™) with three-dimensional ultrasound. To adjust for fetal weight (Wt) and gestational age (GA), UPR_Wt and UPR_SD were calculated using the following formulae: UPR_Wt = measured UPR/estimated fetal weight and UPR_SD = (measured UPR − mean UPR for each GA)/SD of UPR for each GA.*

Results *The AFI was increased significantly in Groups 1 and 2 compared with Group 3. However, the median fetal UPR in Group 1 did not differ from that of Group 3, in contrast to the higher median fetal UPR in Group 2 compared with Groups 1 and 3; this difference remained significant after adjusting for GA and estimated fetal weight in terms of UPR_SD and UPR_Wt. In Groups 2 and 3, AFI and UPR had a positive correlation in terms of UPR, UPR_SD and UPR_Wt.*

Conclusions *Our findings that fetal UPR is significantly increased in cases with increased AFI without fetal anomalies, but not in those with increased AFI and fetal anomalies involving decreased GI absorption of AF, might be used to differentiate causes of increased AF volume. In the absence of fetal anomalies, AFI and fetal UPR correlate positively. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Polyhydramnios is diagnosed in about 1% of pregnancies[1,2]. Although two-thirds of cases are idiopathic, the others are associated with various obstetric complications, such as maternal diabetes, fetal anomalies or multifetal gestation[2]. In certain types of fetal anomaly, such as cleft lip and palate, esophageal atresia and duodenal atresia, the most likely reason for polyhydramnios is considered to be impairment of fetal swallowing or of absorption of amniotic fluid (AF) in the gastrointestinal (GI) tract, while in diabetic women it is thought to originate from increased fetal urinary production as a result of fetal hyperglycemia. In cases of anencephaly, it is thought to be caused by increased transudation of fluid from the exposed meninges into the amniotic cavity or excessive urination caused by the lack of antidiuretic effect due to impaired arginine vasopressin secretion[3].

In spite of these theoretical explanations, there have been few studies on the mechanism of polyhydramnios. AF volume is determined by several factors[4], and any disturbance in the regulatory mechanism can induce polyhydramnios. Fetal urine production can be measured by serial assessment of bladder volume with two-dimensional[5–18] and, as described more recently,

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three-dimensional[19–22] ultrasound. We undertook this study to evaluate whether measurement of the urine production rate (UPR) in fetuses with increased AF volume can be used to differentiate the causes of polyhydramnios.

METHODS

In this cross-sectional study, we enrolled singleton pregnancies with a diagnosis of increased amniotic fluid index (AFI), defined as AFI $\geq$ 18 cm, between November 2005 and February 2009 in Seoul National University Hospital. Targeted sonography was performed to detect associated anomalies and cases were divided into two groups according to their presence or absence of fetal anomalies: Group 1 ($n = 14$) included the increased AFI cases with fetal anomalies thought to be associated with impairment of fetal swallowing or of GI absorption of AF; Group 2 ($n = 43$) included the increased AFI cases without fetal anomalies and included pregnancies affected by maternal diabetes. Cases with increased AFI and fetal anomalies not involving impairment of fetal swallowing or decreased GI absorption of AF were excluded from analysis. For the control group (Group 3, $n = 96$) we enrolled normal pregnant women with normal AFI, defined as $8 \leq$ AFI < 18, and with no fetal anomalies or medical or obstetric complications, such as pre-eclampsia, diabetes, maternal vascular disease, which might affect AF volume. Inclusion criteria for both case and control groups were: singleton pregnancy, live fetus at 24–42 weeks' gestation, and absence of labor and rupture of membranes at the time of measurement. This study was approved by the institutional review board of Seoul National University Hospital.

Obstetric ultrasonographic examinations were performed to measure fetal biometry, AFI and fetal UPR. The measurement of AFI was performed according to the method originally described by Phelan *et al.*[23]. To determine fetal UPR, the fetal bladder volume was measured serially using the rotational Virtual Organ Computer-aided AnaLysis (VOCAL™) method with a 3D Accuvix XQ (Medison, Seoul, Korea) ultrasound machine, according to methods described previously[19]. Briefly, after measuring bladder volume serially two to four times, with a median interval of 5 min, we applied the following formula to calculate fetal UPR: UPR (mL/h) = (second bladder volume − first bladder volume) × ($60/x$), where x is the time interval in minutes between bladder volume measurements. (When more than two bladder volume measurements were made, the mean of the resulting UPRs was used.) All measurements of bladder volume were performed by one of two experienced operators (S.K.P. and E.J.L.). Intra- and interobserver variability was assessed by examining 19 cases selected arbitrarily, each being measured three times by each examiner. To adjust for fetal weight, UPR was divided by the estimated fetal weight: (UPR_Wt) = measured UPR/estimated fetal weight. To adjust for gestational age (GA), we used multiples of the standard deviation of UPR: UPR_SD = (measured UPR − mean UPR at that GA)/SD of UPR at that GA. UPR reference values (mean and SD for each GA) were derived from the previously reported data of normal singleton pregnancies recruited from the routine antenatal clinic of our hospital[19].

Statistical analysis was performed using SPSS version 12.0.1 (SPSS Inc., Chicago, IL, USA). Differences were evaluated using the Mann–Whitney *U*-test or Fisher's exact test as appropriate. Kruskal–Wallis analysis of variance was used for comparison of continuous variables among groups. To examine intra- and interobserver variability, intraobserver and interobserver intraclass correlation coefficients (ICCs) were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Among the 14 cases in Group 1, the fetal anomalies were as follows: cleft lip and palate ($n = 3$), congenital diaphragmatic hernia ($n = 1$), duodenal atresia ($n = 4$), esophageal atresia ($n = 1$), congenital cystic adenomatoid malformation ($n = 1$), ventriculomegaly (lissencephaly, $n = 1$), fetal ascites ($n = 1$) and neck mass or lymphangioma ($n = 2$). We excluded three cases from Group 2 in which congenital anomalies were diagnosed by postnatal examination (atrial septal defect with pulmonary stenosis ($n = 1$), atrial septal defect ($n = 1$), and second brachial cyst in neck ($n = 1$)) and only the remaining 40 cases were included in the analysis.

Table 1 presents maternal characteristics and perinatal outcomes. There were no differences in clinical characteristics, including maternal age, parity, GA at measurement, estimated fetal weight and GA at delivery, among the three groups. However, the median neonatal birth weight in Group 1 was significantly lower than that in Groups 2 and 3.

Table 2 summarizes the AFI and fetal UPR results of each group. AFI was significantly increased in Groups 1 and 2 compared with Group 3 (controls). While there was no significant difference in fetal UPR between Group 1 and Group 3, in Group 2 it was significantly higher than in both Groups 1 and 3, both before and after adjustment for GA or estimated fetal weight.

To determine the best cut-off value for differentiation between Groups 1 and 2, we constructed a receiver–operating characteristics curve to describe the performance of UPR_Wt (area under the curve, 0.729; SE, 0.081; $P < 0.05$). UPR_Wt < 21.5 mL/h/kg had a sensitivity of 92.9%, a specificity of 45%, a positive predictive value of 37.1% and a negative predictive value of 94.7% for the identification of fetal anomalies associated with impairment of fetal swallowing or decreased GI absorption of AF as a cause of increased AFI.

In the study population as a whole, the AFI and fetal UPR were not significantly correlated. However, in women without fetal anomalies (Group 2 and controls), AFI and UPR were positively correlated both before and after adjusting for GA and estimated fetal weight (UPR, $r = 0.191$, $P < 0.05$; UPR_SD, $r = 0.239$, $P < 0.01$; and UPR_Wt, $r = 0.187$, $P < 0.05$ (Figure 1)). There were no

Table 1 Maternal characteristics and perinatal outcomes of patients with increased amniotic fluid index (AFI ≥ 18 cm) and fetal anomalies thought to be associated with decreased swallowing or gastrointestinal absorption of AF (Grp 1), patients with increased AFI and no fetal anomalies (Grp 2) and normal controls (Grp 3, 8 ≤ AFI < 18 cm)

Characteristic	*Grp 1* (n = *14*)	P *(Grp 1 vs. 3)*	*Grp 3* (n = *96*)	P *(Grp 2 vs. 3)*	*Grp 2* (n = *40*)	P *(Grp 1 vs. 2)*	P *(Grp 1 vs. 2 vs. 3)*
Maternal age (years)	31 (30–33)	NS	31 (30–34)	NS	32 (30–35)	NS	NS
Nulliparous	9 (64.3)	NS	54 (56.3)	NS	21 (52.5)	NS	NS
GA at measurement (weeks)	35.0 (31.4–36.9)	NS	34.4 (30.7–37.4)	NS	34.9 (32.4–38.0)	NS	NS
EFW at measurement (g)	2255 (1323–2751)	NS	2313 (1595–2999)	NS	2512 (1951–3215)	NS	NS
GA at delivery (weeks)	39.9 (38.0–40.9)	NS	40.0 (39.0–40.9)	NS	39.3 (38.4–40.4)	NS	NS
Birth weight (g)	3030 (2655–3140)	< 0.005	3260 (3100–3530)	NS	3420 (3110–3730)	< 0.005	< 0.005

Data are given as median (interquartile range) or *n* (%). EFW, estimated fetal weight; GA, gestational age; Grp, Group; NS, not significant.

Table 2 Fetal urine production rate (UPR) and amniotic fluid index (AFI) in patients with increased amniotic fluid index (AFI ≥ 18 cm) and fetal anomalies thought to be associated with decreased swallowing or gastrointestinal absorption of AF (Grp 1), patients with increased AFI and no fetal anomalies (Grp 2) and normal controls (Grp 3, 8 ≤ AFI < 18 cm)

Parameter	*Grp 1* (n = *14*)	P *(Grp 1 vs. 3)*	*Grp 3* (n = *96*)	P *(Grp 2 vs. 3)*	*Grp 2* (n = *40*)	P *(Grp 1 vs. 2)*	P *(Grp 1 vs. 2 vs. 3)*
AFI (cm)	24 (20 to 31)	< 0.001	13 (11 to 16)	< 0.001	20 (19 to 24)	NS	< 0.001
UPR (mL/h)	19.9 (10.8 to 53.1)	NS	30.0 (13.7 to 45.2)	< 0.001	45.4 (28.0 to 67.6)	< 0.05	< 0.005
UPR_SD	−1.06 (−1.21 to −0.07)	NS	−0.58 (−0.99 to −0.20)	< 0.001	0.03 (−0.46 to 0.66)	< 0.01	< 0.001
UPR_Wt (mL/h/kg)	10.8 (7.4 to 19.2)	NS	12.1 (8.4 to 17.4)	< 0.001	19.8 (13.0 to 27.2)	< 0.05	< 0.005

Data are given as median (interquartile range). Grp, Group; NS, not significant; UPR_SD = (measured UPR − mean UPR at that GA)/SD of UPR at that GA; UPR_Wt = urine production rate/estimated fetal weight.

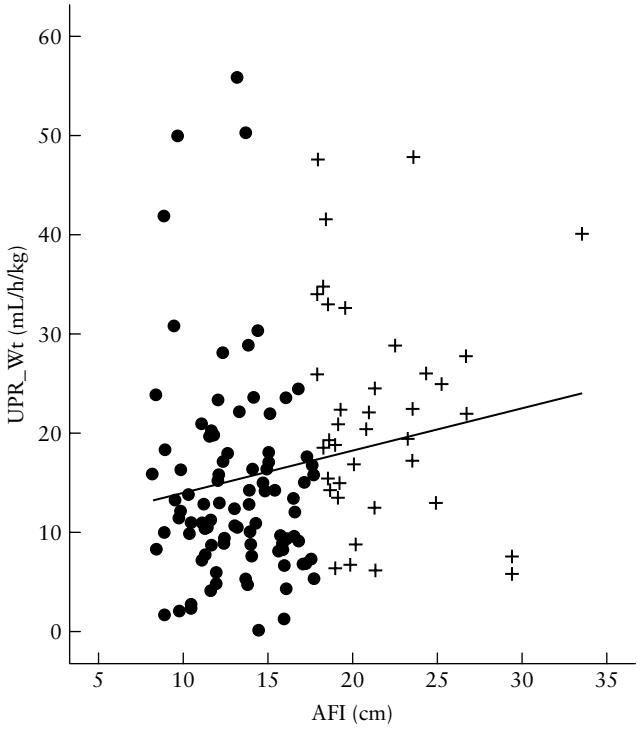

Figure 1 Relationship between fetal urine production adjusted for fetal weight (UPR_Wt) and amniotic fluid index (AFI) in Group 2 (+) and Group 3 (controls) (●) ($r = 0.187$, $P < 0.05$).

significant correlations between AFI and UPR, UPR_SD or UPR_Wt, when analyzing Groups 2 and 3 separately ($P > 0.1$).

Regarding intraobserver variability, the ICCs between the three repeated measurements were 0.999 (range, 0.998–1.000) for Examiner 1 and 0.998 (range, 0.997–0.999) for Examiner 2. The ICC between measurements made by the two examiners (interobserver variability) was 0.999 (range, 0.997–1.000). Figure 2 shows the Bland–Altman plots[24] and 95% limits of agreement between the two examiners for bladder volume measurements.

DISCUSSION

The principal findings of this study were: (1) fetal UPR was significantly increased in cases with increased AFI without fetal anomalies, while it was not in cases with increased AFI and fetal anomalies associated with impairment of fetal swallowing or decreased GI absorption of AF; (2) in cases without fetal anomalies, AFI and fetal UPR were positively correlated. The difference in fetal UPR between the groups may be used for differentiating the causes of increased AF volume: increased volume without fetal anomalies may be caused by increased fetal urinary production, while in the presence of fetal anomalies the cause may be regulatory mechanisms other than increased urine production.

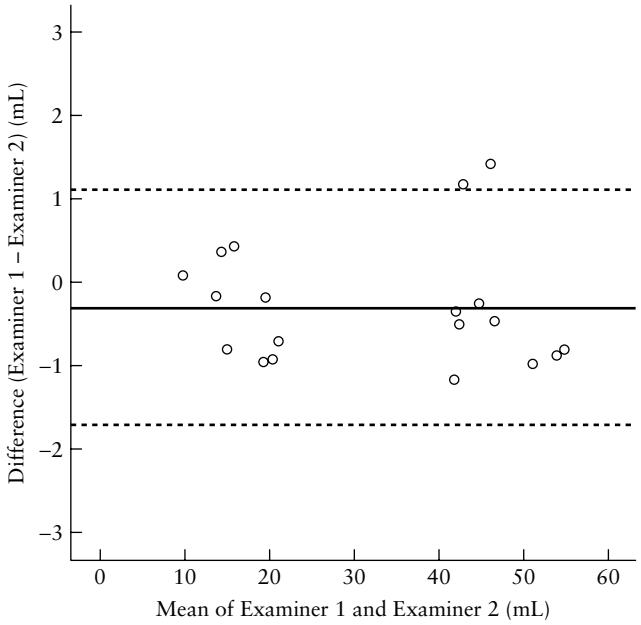

Figure 2 Bland–Altman plot of difference in fetal bladder volume measurements (Examiner 1 – Examiner 2) against their average, with 95% limits of agreement (−1.712 to 1.103 mL/h).

In human pregnancy, some regulatory mechanisms of AF volume are difficult to measure. For quantification of fetal swallowing early human studies used techniques that are no longer appropriate, such as X-ray amniographs or intra-amniotic injection of radioactive substances or colloidal gold[25]. Van den Brink *et al.*[26] showed that reliable quantification of swallowing activity by ultrasound is impossible, even when B-mode color flow and B/M-mode flow measurements are used. Other mechanisms, including secretions from fetal lung or oral–nasal cavities and the intramembranous/transmembranous pathway are also impossible to measure at present. Thus, measurement of fetal UPR is apparently the only feasible means of investigating the regulatory mechanisms of AF volume.

While several investigators have measured human fetal urine production in cases with polyhydramnios, the results have been conflicting. Abramovich *et al.*[27] showed that fetal UPR did not differ between normal pregnancies and those with polyhydramnios, while Kirshon[28] found increased fetal urine output in two cases with idiopathic polyhydramnios and normal urine output in three cases with upper GI obstruction. Kurjak *et al.*[13] found normal fetal UPR in anencephalic fetuses. Touboul *et al.*[29], in their study of 24 cases with idiopathic polyhydramnios, measured the UPR in one case and found it to be five times the normal value for GA. Our findings of increased fetal UPR in idiopathic polyhydramnios in contrast to normal UPR in polyhydramnios with fetal anomalies are consistent with the latter three studies.

Regarding polyhydramnios with diabetes, a sheep model showed maternally induced fetal hyperglycemia to cause fetal glycosuria and diuresis[30]. However, the results of studies of human fetuses in maternal diabetic pregnancies have not been consistent. Yasuhi *et al.*[31] showed increased fetal UPR in diabetic women in a fasting state, whereas van Otterlo *et al.*[11] and Kurjak *et al.*[13] could not demonstrate consistently increased UPR in pregnancies complicated with diabetes. In our study, fetuses in the subgroup of diabetic women in Group 2 ($n = 5$) had increased AFI and UPR_SD compared with controls ($P < 0.05$, data not shown).

Interpretation of our findings should take into account the following points. First, the proportion of fetal anomalies in cases with increased AF volume in our study was about 26% (14 of 54 cases). This is a higher proportion than the reported 8.4% in the population-based study of Biggio *et al.*[1]. A possible reason is that our study included only women attending a single tertiary referral hospital (Seoul National University Hospital), which would have caused selection bias in the study population. Population-based research with a greater number of cases should be performed to consolidate our results.

Second, we defined increased AFI as AFI ≥ 18 cm, although the general definition of polyhydramnios[3] is AFI > 24 or 25 cm. This cut-off point was set so as to enhance the sensitivity of AFI and to avoid missing cases of polyhydramnios. In addition, Phelan *et al.*[23] reported normal AFI at term to be 12.9 ± 4.6 cm, leading us to define normal AFI in this study as $8 \leq$ AFI < 18 cm. Thus, our cases with increased AFI but no fetal anomalies (Group 2) might not represent cases with typical idiopathic polyhydramnios (those with AFI > 24 or 25 cm). Touboul *et al.*[32] recently reported that 17 of 30 (56.7%) fetuses with unexplained polyhydramnios (defined as AFI ≥ 24 cm) had fetal UPR $> 95^{th}$ percentile, and fetuses with UPR $> 95^{th}$ percentile had an increased risk of pathology diagnosed or persistent after the neonatal period. We too found a high proportion of fetuses with increased UPR, yet the magnitude of increase in UPR differed between our study and theirs, only three cases in our Group 2 having UPR $> 90^{th}$ percentile. This difference might be due to our different definitions of increased AFI (AFI ≥ 24 cm vs. AFI ≥ 18 cm). We did not evaluate neonatal outcome according to fetal UPR, because long-term follow-up was not always available in the study population. Our control group had a median UPR_SD of −0.58, lower than that of our previous study[19]. The different definitions of the control groups may have contributed to this discrepancy: AFI was not measured routinely in the previous study and cases with AFI ≥ 18 cm may have been included in the control group. In the current study, only cases with $8 \leq$ AFI < 18 cm were included in the control group.

Third, we defined a cut-off value of UPR_Wt < 21.5 mL/h/kg for the identification of fetal anomalies associated with impairment of fetal swallowing or decreased GI absorption of AF as a cause of increased AFI, with a high sensitivity (92.9%) but a low specificity (45%) and positive predictive value (37.1%). This low specificity should be borne in mind, and careful anatomical ultrasound examination should be considered a priority in clinical application.

In conclusion, we have demonstrated that fetal UPR is significantly increased in cases with increased AFI without fetal anomalies, but not in cases with increased AFI with fetal anomalies involving impairment of fetal swallowing or decreased GI absorption of AF. This suggests that clinicians should focus on more targeted sonography for fetal anomalies in cases with increased AF volume without increased fetal UPR.

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