Relation of rate of urine production to oxygen tension in small-for-gestational-age fetuses

K. H. Nicolaides, MD, M. T. Peters, MD, S. Vyas, MD, R. Rabinowitz, MD, D. J. D. Rosen, MD, and S. Campbell, MD

London, England

Hourly fetal urine production rate was determined by real-time ultrasonography immediately before cordocentesis for blood gas analysis in 27 small-for-gestational-age fetuses at 20 to 37 weeks' gestation; in 14 cases there was associated oligohydramnios. The values were compared with those of 101 appropriate-for-gestational-age fetuses. The hourly fetal urine production rate was significantly lower in the small-for-gestational-age fetuses than in the appropriate-for-gestational-age fetuses. Furthermore, there was a significant correlation between the degree of decrease in urine production and both the degree of fetal hypoxemia and the degree of fetal smallness. There was no significant difference between the oligohydramnios and nonoligohydramnios groups in either the degree of decrease in urine production or the degree of fetal hypoxemia. (Am J Obstet Gynecol 1990;162:387-91.)

Key words: Hourly fetal urine production rate, cordocentesis, fetal blood Po_2, small for gestational age, oligohydramnios

In uteroplacental insufficiency, fetal oxygenation, nutrition, and growth are impaired.[1] In response to fetal hypoxemia there is a redistribution of fetal blood flow, with blood shunted to the brain, heart, and adrenals at the expense of the viscera.[2-4] One of the consequences of this redistribution is that there is reduced renal perfusion and subsequent decreased urine production, which may account for the oligohydramnios seen in this condition.[4, 5] Indeed, oliguric renal failure in growth-retarded neonates may be a result of intrauterine hypoxia and reduction in fetal renal blood flow.[6]

Hourly fetal urine production rate (HFUPR) can be determined by ultrasonography from serial measurements of bladder volumes.[7, 8] The aim of this study is to examine the relationship between HFUPR and fetal blood oxygen tension, measured at cordocentesis.

Patients and methods

HFUPR was determined immediately before cordocentesis in 27 women with small-for-gestational-age (SGA) fetuses at 20 to 37 weeks' gestation. Gestational age was determined by Nägele's rule or an ultrasonographic scan in early pregnancy if the menstrual dates were uncertain. These patients were referred to our unit between June and December 1988 for fetal karyotyping and blood gas analysis because of ultrasonographic evidence of severe growth retardation. Ultrasonographic examination confirmed that in each case the fetal abdominal circumference (AC) was below the 2.5th percentile of our normal range for gestation. Furthermore, in 14 cases there was associated oligohydramnios.[5] Continuous-wave Doppler studies (Doptek spectrum analyzer, Chichester, England) of the uterine artery were performed in all cases. The impedance to flow was considered to be increased if in the flow velocity waveform from either of the uterine arteries there was a notch in early diastole or the resistance index value was above the 97.5th percentile of our reference range. Increased impedance was found in 20 (74%) of the cases.

With the mothers in a semirecumbent position, real-time ultrasonography (Hitachi EUB 340, 3.5 MHz curvilinear transducer; Sonotron, London, England) was used to obtain serial measurements of the longitudinal, transverse, and anteroposterior diameters of the fetal bladder.[7, 8] Measurements were made at 2- to 5-minute intervals for a period of 30 to 40 minutes. Bladder volume was calculated from the three measured diameters with the formula for an ovoid sphere. For each fetus all bladder volumes during the filling phase of the first cycle were plotted against time and the HFUPR was calculated by regression analysis. The end of a cycle was defined either by the observation of micturition or by the observation of dynamic changes in the bladder including reduction in lumen size and increase in wall thickness; the volume immediately before the end of

From the Harris Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, King's College School of Medicine.

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Reprint requests: Kypros H Nicolaides, MD, Harris Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, King's College School of Medicine, Denmark Hill, London SE5 8RX, England.

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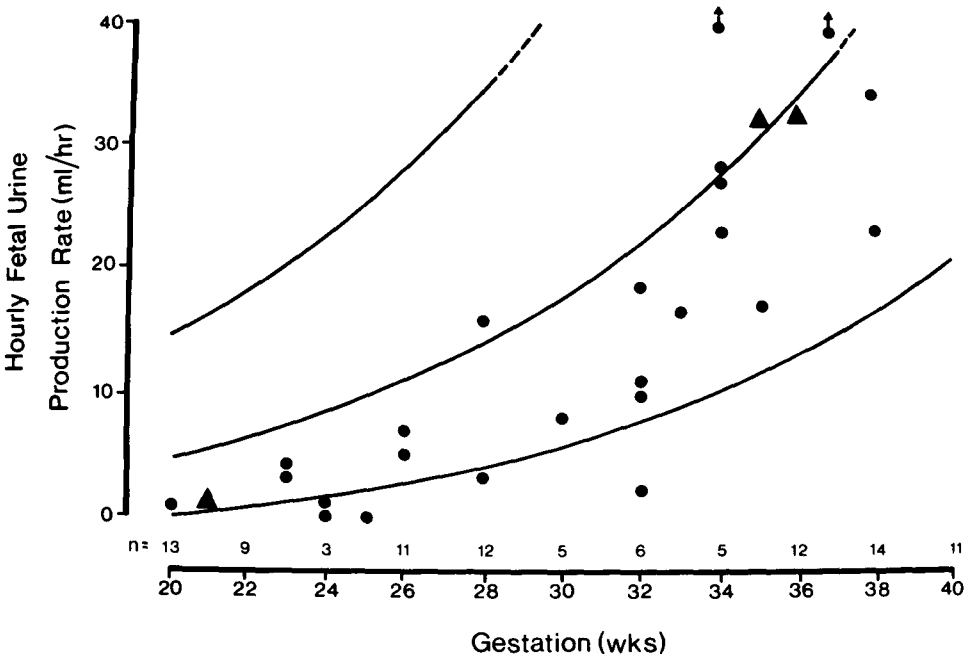

Fig. 1. Hourly fetal urine production rate in 27 SGA fetuses (chromosomes abnormal, ▲; normal, ●) plotted on reference range (mean and individual 95% confidence intervals) that was constructed from study of 101 normal pregnancies.

the cycle was defined as the maximum bladder volume.[8] The intraobserver coefficient of variation for the measurement of bladder volume in each fetus was obtained by dividing the residual SD by the mean of the bladder volumes used for the calculation of HFUPR. The median for all fetuses was 15.4% (range, 4% to 46%). In 24 cases the HFUPR was calculated from the bladder volume measurements obtained by the same observer during two consecutive filling phases; there was no significant difference (the Student paired t test, $t = 0.39$, $p = 0.7$) in HFUPR between the first and second cycles (mean = 30.312 ml/hr, SD = 25.817 and mean = 29.650 ml/hr, SD = 25.683, respectively).[8]

A reference range of HFUPR with gestation was determined from the study of 101 normal singleton pregnancies recruited from the routine antenatal clinic of our hospital. In all cases the fetuses were found by ultrasonographic examination to be structurally normal and to have an AC that was appropriate for gestational age (AGA). The data from the first 85 patients were previously reported.[8]

Cordocentesis was performed as an outpatient procedure without maternal fasting or sedation. The umbilical cord vessel sampled was identified as vein or artery by the ultrasonographically detected turbulence produced after the intravascular injection of normal saline solution (0.4 ml).[9] Fetal blood (1.4 ml) was collected into heparinized syringes; 0.2 ml was used for measurement of blood gases (Radiometer ABL 330 blood gas analyzer, Copenhagen, Denmark), 0.2 ml was used for Kleihauer testing, which confirmed the fetal origin of the sample, and 1 ml was used for karyotyping.

Statistical analysis. Statistical analysis was performed with the Statistical Package for Personal Computers (Timberlake Clarke Ltd., London, England). In the AGA group, the distribution of the data of HFUPR with gestation was made gaussian by logarithmic transformation. The relationship between $\log_{10}$ (HFUPR + 1.5) and gestation was adequately described by a linear model. To produce the reference ranges of HFUPR in milliliters per minute with gestation, the limits of the calculated reference range in logarithms were subjected to an antilogarithmic transformation. Because in AGA fetuses blood Po_2[10] and HFUPR change with gestation, in SGA fetuses these parameters were expressed as the number of SDs by which the observed values differed from the corresponding normal mean for gestation (ΔPo_2, ΔHFUPR, and ΔAC, respectively).

In the SGA fetuses, regression analysis was performed to test for any significant correlation between fetal ΔPo_2, ΔHFUPR, and ΔAC. The Student unpaired t test was applied to test for any differences in the HFUPR between the AGA and SGA groups and for differences in HFUPR or Po_2 between the oligohydramnios and nonoligohydramnios subgroups.

Table I. Fetal urine production and blood Po_2 (expressed as SDs from the normal mean for gestation), karyotype, and outcome in 27 SGA fetuses

Case no.	Gestational age (wk)	Karyotype	ΔPo_2	$\Delta HFUPR$	Amniotic fluid volume	Delivery			
						Gestational age (wk)	Outcome	Birth weight (gm)	Birth weight %
1	19*	46,XX	−4.22	−2.10	Oligohydramnios	21	Intrauterine death	140	—
2	21	69,XXY	−2.77	−1.93	Oligohydraminos	22	Termination of pregnancy	217	—
3	23*	46,XY	−2.74	−1.31	Reduced	23	Termination of pregnancy	196	—
4	23*	46,XY	−2.35	−0.45	Oligohydramnios	28	Intrauterine death	750	<3
5	24*	46,XX	−3.93	−4.05	Oligohydramnios	24	Intrauterine death	300	<3
6	24*	46,XX	−1.97	−2.24	Oligohydramnios	29	Live birth	560	<3
7	25*	46,XY	−2.51	−4.30	Oligohydramnios	30	Live birth	650	<3
8	26*	46,XX	−2.75	−1.41	Oligohydramnios	32	Intrauterine death	660	<3
9	28*	46,XY	−1.97	−0.78	Oligohydramnios	29	Live birth	540	<3
10	28*	46,XX	−2.09	−3.25	Reduced	28	Live birth	834	<10
11	28	46,XX	−2.37	0.36	Reduced	28	Live birth	810	<10
12	30*	46,XX	−3.42	−1.47	Normal	30	Live birth	1077	<10
13	31*	46,XY	−3.08	−3.42	Normal	32	Live birth	850	<3
14	32*	46,XX	−2.50	−1.35	Normal	32	Live birth	1020	<3
15	32*	46,XY	−1.60	−0.22	Oligohydramnios	34	Live birth	1540	<3
16	32*	46,XX	−2.82	−0.31	Reduced	32	Live birth	1100	<3
17	33*	46,XY	−2.43	−0.75	Normal	33	Live birth	1700	<10
18	34	46,XX	−1.82	−0.15	Oligohydramnios	34	Live birth	1418	<3
19	34	46,XY	−0.58	1.13	Normal	38	Live birth	2050	<3
20	34*	46,XY	−2.16	0.07	Normal	35	Live birth	1808	<3
21	34*	46,XY	−0.63	−0.35	Oligohydramnios	38	Live birth	2155	<3
22	35*	46,XY	−3.04	−1.08	Oligohydramnios	35	Live birth	1358	<3
23	35	47,XY,+21	−1.52	0.10	Normal	36	Intrauterine death	1700	<3
24	36*	47,XX,+18	−0.59	0.07	Reduced	37	Live birth	1450	<3
25	37	46,XX	−0.94	2.14	Reduced	39	Live birth	1998	<3
26	38*	46,XY	−0.99	−1.29	Oligohydramnios	39	Live birth	1786	<3
27	38	46,XY	−0.60	−0.50	Oligohydramnios	40	Live birth	2120	<3

The birth weight percentile was calculated from the nomograms of Yudkin et al.[17]
*Abnormal uterine artery Doppler ultrasonography.

Results

In the AGA fetuses HFUPR increased significantly with gestation from a mean value of 4.5 ml/hr at 20 weeks' to 54 ml/hr at 40 weeks' gestation (Fig. 1). The correlation was best described by the equation:

$$\log_{10}(\text{HFUPR} + 1.5) = -0.177 + 0.048 \times \text{weeks' gestation}$$
$$(r = 0.863,\ n = 101,\ p < 0.0001,\ \text{SD} = 0.197).$$

The data on HFUPR, Po_2, karyotype, outcome, and birth weight of the 27 SGA fetuses are shown in Table I. The mean abdominal circumference was 5.4 (range, 3.1 to 7.8) SDs below the normal mean for gestation. In all cases the fetal growth retardation was asymmetrical [mean head circumference/abdominal circumference = 5.75 (range, 2.44 to 10.34) SDs above the normal mean for gestation]. Although in 20 cases the amniotic fluid volume was subjectively assessed by ultrasonography as being reduced, the criteria for oligohydramnios were met in only 14 of the cases.[5] In 16 of these 27 highly preselected cases the Po_2 was >2 SDs below the normal mean for gestation. Three of the fetuses were chromosomally abnormal. All the fetuses were structurally normal including the three aneuploidies. Of the 27 pregnancies, 20 resulted in a live birth, 2 were terminated electively (one fetus was triploid and the other was severely growth retarded and hypoxemic at 23 weeks' gestation), and 5 resulted in an intrauterine death (one fetus was chromosomally abnormal and 4 were severely growth retarded and hypoxemic and died 1 to 6 weeks after cordocentesis).

In the SGA fetuses the mean HFUPR was lower than that of the AGA fetuses (Fig. 1; mean difference = 1.068, SEM = 0.287, $t = 3.72$, $p < 0.001$).

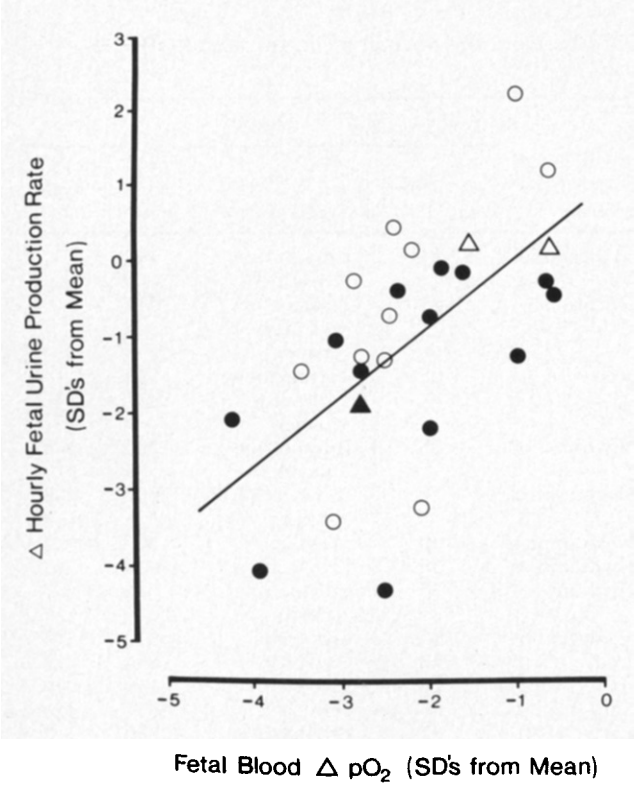

Fig. 2. Relationship between fetal urine production rate (in SDs from normal mean for gestation) and fetal blood Po_2 (in SDs from normal mean for gestation) in 27 SGA fetuses (abnormal karyotype, Δ and ▲; oligohydramnios, ● and ▲; nonoligohydramnios, ○ and Δ).

Furthermore, there were significant correlations between ΔHFUPR and both ΔPo_2 (Fig. 2; $r = 0.60$, $n = 27$, $p < 0.001$) and ΔAC ($r = 0.59$, $n = 27$, $p < 0.01$). There was no significant correlation between ΔPo_2 and ΔAC ($r = 0.327$). Multiple regression analysis showed that the combination of ΔPo_2 and ΔAC explained 53.4% of the variance in ΔHFUPR [ΔHFUPR = 3.008 + 0.681 (ΔPo_2) + 0.478 (ΔAC); residual SD = 1.061].

Comparison between the oligohydramnios ($n = 14$) and nonoligohydramnios ($n = 13$) subgroups showed no significant difference in ΔHFUPR (mean difference = 0.875, SEM = 0.560, $t = 1.56$) or ΔPo_2 (mean difference = 0.112, SEM = 0.39, $t = 0.29$).

Comment

In AGA fetuses the HFUPR increases with gestation and the values are approximately double those reported in previous studies.[11-13] The reason for this discrepancy is that the cycle length is shorter than the mean of 110 minutes reported by Campbell et al. and therefore in preceding studies fetal bladder measurements were made at insufficiently frequent intervals.[7, 8]

In SGA fetuses the HFUPR is significantly lower than that in AGA fetuses. Furthermore, there is a significant correlation between the decrease in urine production and the degree of fetal hypoxemia. We have previously shown that in hypoxemic SGA fetuses impedance to flow in the renal artery is increased.[1] These data provide further evidence that in fetal hypoxemia there is redistribution in blood flow with decrease in renal perfusion and consequent decrease in HFUPR; this may eventually lead to fetal organ failure.[6] Wladimiroff and Campbell[11] also showed lower HFUPR in SGA than in AGA fetuses, but found no correlation between antepartum HFUPR and the incidence of fetal distress during labor or 1-minute Apgar scores; however, the latter two events do not necessarily reflect antepartum fetal oxygenation.

Kurjak[12] examined 70 SGA fetuses and found the HFUPR to be below the 10th percentile of the normal in 59%, and below the 5th percentile in an additional 33% of the cases. Those fetuses with the lowest urine production rate were also the most growth retarded. In our group of SGA fetuses, ΔHFUPR was significantly associated with both the degree of fetal smallness and fetal hypoxemia. This suggests that factors such as redistribution of blood flow, in addition to fetal size, must have caused the observed relative oliguria. Indeed, the fact that HFUPR and Po_2 are similarly correlated in the group of chromosomally abnormal fetuses suggests that urine production reflects fetal oxygenation regardless of the primary pathology leading to intrauterine growth retardation.

Amniotic fluid is predominantly a result of fetal urine production and is related to renal perfusion.[14] Reduced amniotic fluid volume is associated with poor perinatal outcome.[15] However, amniotic fluid volume is similar to biometric fetal measurement in that it reflects the chronic state of fetal well-being rather than the current state of fetal oxygenation.[16] In view of this, the lack of a significant difference in Po_2 between the oligohydramnios and nonoligohydramnios groups is not surprising. Furthermore, in the evaluation of fetal well-being, the inability to accurately measure amniotic fluid volume has led to the adoption of the all or none qualitative definition of oligohydramnios by the 1 cm rule.[5] In contrast, measurement of HFUPR is quantitative, and is more likely to reflect the current state of fetal oxygenation. Its value in the assessment of fetal well-being remains to be established.

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Middle cerebral artery blood flow in normal and growth-retarded fetuses

Jean-Claude Veille, MD, and Ilan Cohen, MD
Cleveland, Ohio

Doppler ultrasonography of the middle cerebral artery was performed on 17 fetuses that were small for gestational age at the time of delivery. Results were compared with a group of 25 fetuses that had a normal weight for gestational age at the time of delivery. Despite a significant difference in fetal weight and systolic/diastolic ratio of the umbilical artery between the two groups, no difference was found in either the systolic/diastolic ratio or in the Pourcelot index of the middle cerebral artery. This may reflect a protective effect on the brain circulation in the small-for-gestational-age fetus. (AM J OBSTET GYNECOL 1990;162:391-6.)

Key words: Duplex ultrasonography, normal/abnormal fetal growth

Doppler ultrasonographic techniques have been used to follow up and manage pregnancies complicated by intrauterine growth retardation (IUGR),[1-3] hypertension,[4 5] diabetes mellitus,[6] twin pregnancies,[7 8] Rh immunization,[9] and fetal malformations. With the use of either continuous-wave Doppler technique or pulsed Doppler technique, blood flow in the umbilical artery was evaluated. Recently, combined two-dimensional real-time and pulsed Doppler systems have opened the possibility of studying fetal cerebral blood flow in normal and complicated pregnancies.[10]

The purpose of this study was to assess middle cerebral artery waveform with Duplex ultrasonography in normal pregnancies and in pregnancies complicated with small-for-gestational-age (SGA) fetuses. We hypothesized that in fetuses with IUGR, blood flow to the

From the Department of Reproductive Biology, MacDonald Hospital for Women, Case Western Reserve University.
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