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Original Article

Fetal renal blood flow velocimetry and cerebro-placental ratio in patients with isolated oligohydramnios

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ABSTRACT

Objective: It's proposed that oligohydramnios is caused by decreased renal perfusion due to redistribution of fetal blood at fetal growth restriction. Isolated oligohydramnios refers to the presence of oligohydramnios without fetal structural and chromosomal abnormalities, without fetal growth restriction, without intrauterine infection, and in the absence of known maternal disease. It's unknown whether the redistribution or decreased renal perfusion cause isolated oligohydramnios. The aim of the study was to evaluate fetal renal artery Doppler blood velocimetry and cerebro-placental ratio (CPR) among women with isolated oligohydramnios between 25–40 weeks of gestational age.
Study design: The middle cerebral artery, umbilical artery and, renal artery pulsatility index (PI) values were measured in 45 fetuses with isolated oligohydramnios and 65 fetuses with normal amniotic fluid. Oligohydramnios was defined as deepest vertical amniotic fluid being measured lower than 1 cm. The CPR (middle cerebral artery PI/umbilical artery PI) and renal artery PI values were expressed as multiples of the normal median (MoM) and were compared between the two groups.
Results: There was no difference in MoM of CPR PI ($p = 0.167$) and MoM of renal artery PI values (right $p = 0.253$, left $p = 0.353$) between the groups.
Conclusion: The renal artery Doppler velocimetry and CPR were not significantly different in the women with isolated oligohydramnios, compared to the women with normal amniotic fluid.

Introduction

The incidence of oligohydramnios is reported as 1.5% with routine ultrasound screening [1]. Pathophysiology of oligohydramnios is poorly understood and is controversial.

Oligohydramnios is observed commonly in growth-retarded fetuses. Development of oligohydramnios in intrauterine growth restriction is related to chronic fetal hypoxemia caused by placental insufficiency. In theory, chronic hypoxia and fetal malnutrition induced by poor placental perfusion cause redistribution of cardiac output from periphery to brain [2,3]. Vascular resistance in renal arteries increases and renal blood flow decrease, while the resistance falls in cerebral circulation and flow to brain increases [4–6]. It is suggested that oligohydramnios in fetal growth restriction is caused by decreased urine output due to reduced renal perfusion [3,7–9].

Umbilical artery Doppler indices increase in correlation with degree of injury and hypoxia of placenta [10]. The cerebro-placental ratio (CPR) is a ratio of the chosen Doppler index of middle cerebral and umbilical arteries. It reflects a redistribution of cardiac output to cerebral circulation. It has been claimed to be superior to umbilical artery pulsatility index (PI) in the prediction of adverse perinatal outcome in small gestational aged fetuses [6,11].

An increase in fetal renal artery PI was described in appropriate grown postterm fetuses with oligohydramnios. It's supposed to be caused by redistribution fetal cardiac output [12,13]. In many of cases, oligohydramnios is not accompanied by intrauterine growth restriction, maternal diseases that are known to predispose intrauterine growth restriction or oligohydramnios such as hypertension, diabetes or other vascular diseases, congenital anomalies and postterm pregnancy [1]. These are referred as isolated oligohydramnios and constitute 53% of the cases [1]. Isolated oligohyramnios is considered as a marker of chronic fetal hypoxemia or poor placental functions based on the evidences obtained from postterm and growth-restricted fetuses. Whether isolated oligohydramnios is related to redistribution of cardiac output remains undefined yet [14,15].

The purpose of this investigation was to determine if women with isolated isolated oligohydramnios differ in their CPR and fetal renal artery Doppler waveform analysis from those with a normal volume of amniotic fluid.

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Materials and methods

A prospective case-control study was undertaken in pregnant women of 25–40-weeks of gestational ages, in the Department of Obstetrics and Gynecology at Ataturk University Faculty of Medicine. The study was approved by institutional review board.

In this study, we compared renal artery PI and CPR between women with isolated oligohydramnios and normal controls. The reference range for renal artery PI and CPR change with gestational age [16,17]. In order to adjust for the effect of the gestational age on the measurements, the values for renal artery PI and CPR were expressed as multiples of the median (MoMs). For this purpose, first, we developed reference ranges and median with gestational age for UA-PI, MCA-PI, renal artery PI and CPR and second, converted renal artery PI and CPR to MoMs values and compared them between women with isolated oligohydramnios and normal controls.

Study subjects

The study group consisted of pregnant women between 25–40 weeks of gestation referred to the clinic for evaluation due to oligohydramnios, and women with normal volume of amniotic fluid who attend for antenatal follow-up. Oligohydramnios was defined as single deepest vertical amniotic fluid of lower than 1 cm. Normal volume of amniotic fluid was defined as a single deepest vertical amniotic fluid measured between 2–8 cm. The women were recruited to the study if the following criteria were met: (1) normal fetal anatomy, (2) estimated fetal weight between 10th and 90th percentiles for gestational age (3) normal umbilical artery PI by local reference values estimated by us. The gestational age was determined on the basis of the last menstrual period and was verified by either a first-trimester or early second trimester (<20 weeks) ultrasonography. The women who had chronic hypertension, hypertensive disorders of pregnancy or vascular diseases predisposing to preeclampsia or intrauterine growth retardation, and the women who had rupture of membranes were not included in the study. AmniSure® test was used to document the intact membranes for all women who had oligohyramnios [18].

Eligible women with oligohydramnios were consecutively included in the study after signing the informed consent form. For each two women with oligohydramnios, next three consecutive pregnant women without oligohydramnios were recruited to the control group. The women were followed-up to delivery and those with abnormal fetal anatomy, a neonatal birth weight of lower than 10th percentile for gestational age (i.e Small for Gestational Age [SGA]) and gender and those who developed hypertensive disease of pregnancy were identified.

Reference ranges for CPR and renal artery pulsatility index

A reference range for CPR (middle cerebral artery PI /umbilical artery PI) and PI of renal artery in fetuses from 20 to 40 weeks of gestation was established from 112 normal fetuses. The gestational age was determined on the basis of the last menstrual period and was confirmed by either a first-trimester or early second trimester (<20 weeks) ultrasonography. All of these women had delivered appropriately grown neonates at $\geq$ 36 weeks without complications.

Doppler studies

Color Doppler flow imaging and pulse Doppler ultrasonography were performed with 2–6 MHz convex transducer (ALOKA α 5 or α 10, ALOKA Co., LTD, Tokyo, Japan) by a single investigator (M.B) to eliminate interobserver variation. Doppler measurements were performed after the amniotic fluid volume estimation. The spatial peak temporal average intensity was below 50 mW per square centimeter and the wall filter was set at 50–100 Hz to preserve the end diastolic component of the waveform. Middle cerebral artery was insonated at close to its origin in the internal carotid artery. Velocity waveforms were obtained from the umbilical artery at the mid-section of the umbilical cord whereas renal artery waveforms were recorded at close to renal hilum.

A good real-time image in which a vessel is situated was obtained and blood flow through the vessel was visualized by color flow Doppler. After a straight segment of the vessel was identified, Doppler gate placed within the lumen of vessel. The angle between the ultrasound beam and the direction of blood flow was kept as close as possible to 0 degrees. When at least five consecutive uniform flow velocity waveforms with a high signal-to-noise ratio were obtained during periods of fetal rest and apnea the image was frozen and the waveforms were quantified using the PI. The intraobserver coefficient of variation for the measurement of PI was determined by 10 consecutive examinations on 10 women within one hour.

Sample size

In the published literature there was no study in which renal artery PI MoM or CPR have been compared between isolated oligohydramnios and normal controls to estimate the sample size. We used two previous report to estimate an effect size [12,15]. We calculated pooled standard deviation as 0,045 and post hoc effect size as 0,54 and from the study by Oz et al. in which renal artery resistance index was compared between postterm women who has isolated oligohydramnios and who has normal amniotic fluid [12]. We calculated pooled standard deviation as 0,28 and post hoc effect size as 0,96 and from the study by Yoshimura et al. in which renal artery pulsatility index was compared between term isolated oligohydramnios and term normal control. We assumed the effect size as 0.6 for renal artery Doppler velocity wave form changings at oligohydramnios. To detect an effect size of 0.6, we needed to enroll 45 women for oligohydramnios group and 65 for control group with allocation ratio of 1.5 for a power of 80% at a significance level of 0.05.

Statistics

Regression analysis was used to calculate reference ranges for CPR and renal artery PI. The values for renal artery PI and CPR were expressed as multiples of the median (MoMs) in order to adjust for the effect of the gestational age on the measurements. MoMs for the CPR value were calculated by dividing the measured value by the expected CPR value for the gestational age as determined with the regression equation. The MoMs for renal artery PI were calculated by similar method. The MoM values for renal artery PI and CPR were compared between the cases and the controls by student's *t*-test For other comparisons, the data were analyzed with the Student's *t*-test and Mann-Whitney U test for continuous variables and Pearson Chi-Square test for categorical variables. The Kolmogorov-Smirnov test was used to check normality of distributions. *Cohen's d* were calculated according to this formula as a measure of effect size: *Cohen's d*= (μ_1- μ_2)/pooled SD. All the tests were 2-sided and p values less than 0.05 were considered statistically significant. Statistical analyses were performed with the SPSS statistical package (SPSS, Chicago) and SigmaPlot 11 (Systat Software Inc., California, USA).

Results

The CPR and renal artery PI in the normal fetuses followed a normal distribution. The expected values for CPR were calculated using the following formula: CPR=−0.0029*(Gestational age)^2+ 0.1906*(Gestational age)−1.5979, (Adjusted $R^2 = 0.32$, $P < 0.001$). The following formula was used to calculate the expected values for renal artery: Renal artery PI= −0.0419*(Gestational age)+2.9057 (Adjusted $R^2 = 0.21$, $P < 0.001$), The intraobserver variability for the PI measurements based on ten examinations was %6.9 for umbilical artery, %8.2 for middle cerebral artery and %8.4 for renal artery.

During the study period, 45 women with oligohydramnios and 65 normal controls were recruited. Ventricular septal defect was detected in two neonates in the control group. On follow-up, preeclampsia was developed in 4 (9%) women in the case group and 1 (2%) in the control group (p = 0.154). The weights of 6 (13%) neonates were below 10th percentile by sex and age at birth in the case group (p = 0.004). All six SGA babies were delivered after 37th gestational week, four of which were delivered at 40th gestational week.

Renal artery PI and CPR of cases and controls with normal reference ranges are shown in Figs. 1–3, respectively. The mean gestational age at Doppler imaging was 34 ± 3 weeks in case group and 36 ± 4 in normal controls. The median interval from Doppler imaging to delivery was 2 (0–16) weeks in the control group and 2 (0–8) in the case group. Fifty-one (% 46) women delivered within one week (22[%49] vs. 29[%45] in case and control groups, respectively, $p = 0.659$).

CPR MoM was not significantly different between women with oligohydramnios and normal controls (0.96 ± 0.21 vs. 1.02 ± 0.19, *Cohen's* $d = 0.3$, $p = 0.167$ respectively, Fig. 3). Similarly, between women with oligohydramnios and normal controls, right renal artery PI MoM (0.95 ± 0.32 vs. 1.03 ± 0.33., *Cohen's* $d = 0.25$, $p = 0.253$, respectively) and left renal artery PI MoM (0.99±0.34 vs. 1.05±0.35 vs., *Cohen's* $d = 0.17$, $p = 0.353$, respectively) values were not significantly different, either (Figs. 1 and 2).

We performed an analysis after excluding the women who developed preeclampsia or delivered a SGA infant or had an infant with ventricular septal defect. A total of 35 women with oligohydramnios were compared to 62 normal controls. CPR MoM and right renal arteries PI MoM values were not different (data not shown).

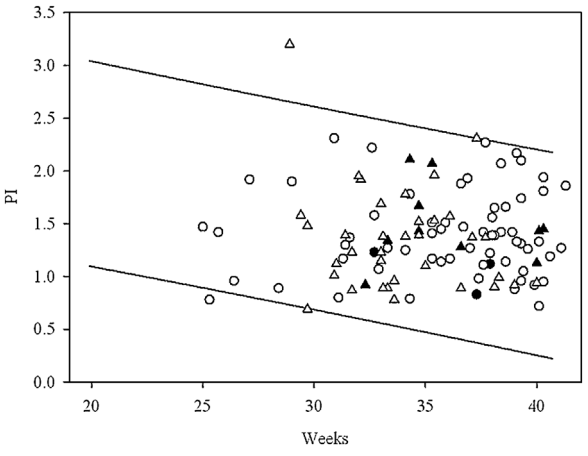

Fig. 1. Right renal artery pulsatility indexes in cases (△, ▲) and controls (○, ●) plotted on the normal reference range (0.95 ± 0.32 vs. 1.03 ± 0.33, p = 0.253, for cases and controls respectively). Black symbols show women had preeclampsia, small for gestational aged infant or an infant with ventricular septal defect.

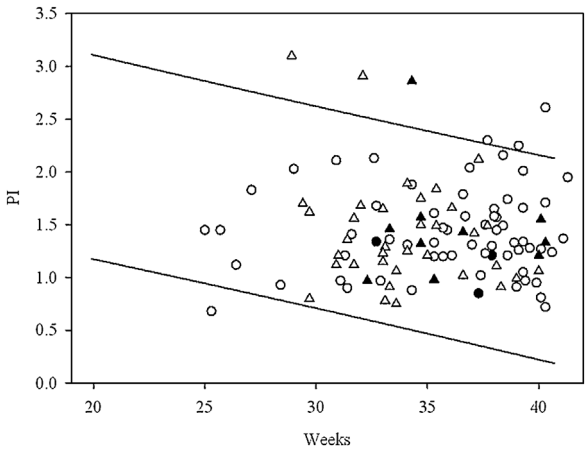

Fig. 2. Left renal artery pulsatility indexes in cases (△, ▲) and controls (○, ●) plotted on the normal reference range (0.99 ± 0.34 vs. 1.05 ± 0.35, p = 0353 for cases and controls respectively). Black symbols show women had preeclampsia, small for gestational aged infant or an infant with ventricular septal defect.

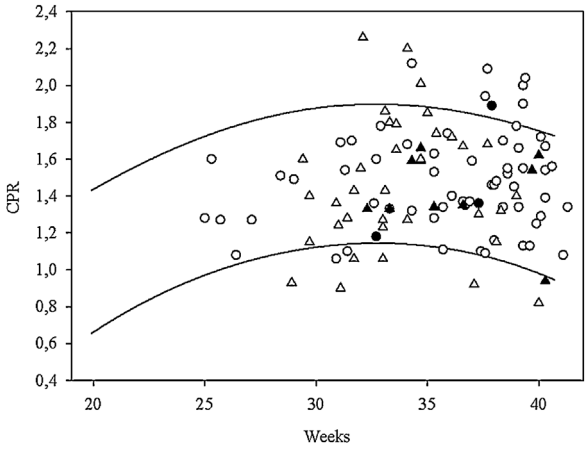

Fig. 3. Cerebro-placental ratio in cases (△, ▲) and controls (○, ●) plotted on the normal reference range (0.96 ± 0.21 vs. 1.02 ± 0.19, p = 0.167 for cases and controls respectively). Black symbols show women had preeclampsia, small for gestational aged infant or an infant with ventricular septal defect.

Discussion

We found that CPR and PI of renal arteries are same between women with isolated oligohydramnios and normal control.

The study has a number of strength. Firstly, we converted Doppler data to MoMs and eliminated effect of gestational age. Secondly, we attempted to eliminate as possible as cases with placental insufficiency. All fetuses with oligohydramnios carry a suspicion of chronic hypoxia depending on placental insufficiency. However, it is impossible to discriminate definitely the fetuses having placental insufficiency from normal fetuses. Doppler velocimetry indexes of the umbilical artery that is used as diagnostic and prognostic tool may not elevate at milder forms of placental vascular dysfunction. The early fetal response to early-onset placental insufficiency is proposed to a failure of the fetus to reach its growth potential. A birthweight that fall in small for gestational age category has been the most widely used criterion for identification growth restriction at birth [19]. Although most of growth restricted fetuses fall in this category, some fetuses with an estimated weight of greater than the 10th percentile demonstrate characteristics of fetal growth restriction [20]. Small for gestational age threshold has also been adopted for the prenatal period by

using an sonographically estimated fetal weight below the 10th percentile as a suspicion of fetal growth retardation. However, ultrasonic estimation of fetal weight deviate approximately 15% around the actual birthweight [21]. In the current study, we excluded not only the cases with an estimated fetal weight lower than 10th percentile but also the cases with an umbilical artery PI above the reference range in order to eliminate cases with placental insufficiency. Estimation of amniotic fluid with ultrasound does not correlate well with actual volume. Oligohydramnios was defined as deepest vertical amniotic fluid being measured lower than 1 cm to increase diagnostic accuracy. At the end of study, a group of fetuses has a birthweight under 10th percentile of their gestational age. This group of fetuses is an expected deviation caused by ultrasonic estimation of fetal weight and may have placental insufficiency. When we excluded this group from analysis, the results did not change.

The study has a number of limitations. First, the post hoc effect size for both CRP and fetal renal artery was a small effect size and it was lower than assumed. The study has not enough power to detect a possible significance if it ever exists. Second, PI values may not exactly reflect the actual blood flow. Milder forms of placental insufficiency, in particular cases close to the term, may not be detected by traditional Doppler methods [22].

Previously, two studies investigated whether redistribution of blood caused oligohydramnios in pregnant women who had no unfavorable fetal or maternal outcome. In accordance with our study, Treger et al. reported no differences in PI of fetal renal, umbilical, middle cerebral arteries between pregnancies with isolated oligohydramnios and normal amniotic fluid index at 24–40 weeks of gestation [14]. However, Yoshimura et al. reported that PI of umbilical artery and renal artery were significantly higher in appropriately grown for age (AGA) fetuses with oligohydramnios compared to fetuses with normal amniotic fluid [15]. That study consisted of 100 AGA and 39 growth retarded fetuses between 36–40 weeks. Authors also reported that PI of umbilical artery and renal artery were significantly higher in growth-retarded fetuses with oligohydramnios compared to fetuses with normal amniotic fluid. The cause of disagreement between that study and the current one is not clear; however, the study populations may differ between the studies. It is possible that we eliminated more effectively the cases with placental insufficiency. In both reports, authors did not adjust Doppler measurements for gestational week but used crude Doppler data. The distributions of Doppler measurements are subject to gestational age [16,17]. We get a more precise result because we used MoMs values for renal artery PI and CPR and, adjusted the effect of the gestational age on the measurements.

The hypothesis that explains oligohydramnios by oliguria due to renal hypoperfusion was challenged [23,24]. In chronic sheep preparation, Gagnon et al. induced chronic hypoxemia and oligohydramnios by placental embolization, but fetal urine production did not change [24]. They proposed that oligohydramnios developed due to increased intramembranous absorption of water in placental insufficiency [25].

Placental dysfunction causes both nutritional deficiency and respiratory hypoxemia. Early-onset placental dysfunction causes fetal growth retardation, while late-onset disease cause respiratory compromise before fetus has time to fail to grow [25]. Markers of fetal hypoxemia may be finding of late-onset placental dysfunction in the fetuses in which fetal size was preserved. CPR at term is supposed to be a marker of fetal hypoxemia secondary to placental dysfunction [26]. However, we did not find a difference between the two groups in terms of CPR. Furthermore, there is no good quality evidence that identify an association between isolated oligohydramnios and intrauterine fetal death [27]. Within limitations of the current study, we propose that idiopathic oligohydramnios is not caused by redistribution of fetal blood.

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Disclosure of interest

Authors declare no conflict of interest.

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