

## Original Investigations

### Maternal serum and urinary carbohydrate antigen 19-9 as a marker in pregnancies with antenatal hydronephrosis: a preliminary and descriptive study

#### Akbaş et al. CA 19-9 levels in antenatal hydronephrosis

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#### Abstract

**Objective:** Fetal hydronephrosis (FH) is the most common fetal renal pathology encountered in the daily obstetric practice. Urinary and serum carbohydrate antigen 19-9 (CA 19-9) levels are higher in obstructive renal pathologies. Our aim was to assess the maternal urinary and serum CA 19-9 levels in pregnancies with FH and compare results with controls.

**Materials and Methods:** 20 pregnancies with severe FH, 20 pregnancies with mild-moderate FH, and 20 healthy singleton pregnancies were included in this descriptive, case-control study. Maternal urinary and serum CA19-9 level were measured and compared between groups.

**Results:** Severe FH cases had significantly higher maternal urinary CA19-9 level compared to control group (Median = 75 vs 24; respectively, U = 8.6, p = 0.014). The difference between mild-moderate FH and control group was not statistically significant in terms of urinary CA 19-9 level. No statistically significant difference was found between the groups with respect to the maternal serum CA 19-9 levels.

**Conclusion:** Our results show that maternal urinary CA 19-9 level is significantly higher in the pregnancies with severe FH but serum CA 19-9 levels were not different between groups. If the mechanisms of transplacental passage and maternal urinary excretion are clarified, maternal urinary CA 19-9 may be a potential marker for pointing fetal kidney damage.

**Keywords:** hydronephrosis; pregnancy; CA-19-9 antigen

#### Introduction

Fetal renal pathologies are frequently encountered in obstetric practice. Fetal hydronephrosis (FH) is the most common antenatally detected renal pathology (1). The severity of hydronephrosis and the need for postnatal treatment are particularly associated with the underlying pathology. The most basic and frequently used technique for evaluation of fetal renal pelvis is the measurement from anterior to posterior in the transverse plane. This measurement depends on the operator and is affected by maternal hydration. Furthermore, it does not provide information about renal parenchymal damage (2,3). Given all these factors, the antero-posterior measurement of the renal pelvis has low prognostic value. Other ultrasonographic measures and urinary markers are not adequate enough for making an accurate diagnosis and predictive enough for clinically significant FH(4). Carbohydrate antigen 19-9 (CA 19-9) is a Lewis blood group antigen derivative glycoprotein (5). This antigen is found in the amniotic fluid in high concentrations due to the secretion of amnion and decidual cells(6). In addition to being a tumor marker used in gastrointestinal cancers, this antigen is increased in many benign conditions. Renal epithelium excrete CA 19-9 in physiological conditions. High serum and urine levels can be detected in patients with severe hydronephrosis (7-9). In the literature, it has been shown that urinary and serum CA 19-9 can be used as a marker for the diagnosis and management of obstructive renal pathologies (10,11). This study was based on the hypothesis that increased levels of CA 19-9 could be detected in maternal serum and urine due to increased excretion by the fetus with hydronephrosis. The research aim was, therefore, to evaluate the CA 19-9 levels in maternal serum and urine in pregnancies with FH.

#### Materials and methods

Sixty pregnant women who were admitted to the Manisa Celal Bayar University, Obstetrics and Gynecology Department between July 2017 and July 2018 were enrolled for this case-control study. Three groups were

described as severe FH group, mild-moderate FH group and control with each group consisting of twenty cases. For the diagnosis of mild-moderate hydronephrosis, the criteria of anteroposterior diameter between 4 and 10 mm (second trimester) or 7 and 15 mm (third trimester) were used. Greater than 10 mm and 15 mm were used for the diagnosis of severe hydronephrosis (second and third trimester, respectively) (12). The control group consisted of twenty healthy pregnant women with matching ages and gestational ages. The Health Ethics Board of Manisa Celal Bayar University approved this study (number = 20.478.486-23248 ; date = 28.06.2017). Informed consent was read and signed by all participants and the study was carried out in compliance with the Declaration of Helsinki.

Multiple gestation, any fetal chromosomal or structural anomaly, pregnancies complicated with any type of diabetes mellitus, gestational or pregestational hypertensive disorders, women with inherited thrombophilia, connective tissue disorders, chronic renal or hepatic disease, history of any proven or suspected malignancy were exclusion criteria of the study.

A complete obstetric history and demographic data were obtained. Antenatal detailed anomaly scan was performed. Maternal peripheral venous blood and urine samples were collected until 10:00 am and after an overnight fasting. Venous blood samples were centrifuged for 15 minutes at 3000g. Quantitative measurement of urinary and serum CA 19-9 levels was performed using original reagents by a two-region immunoenzymatic method on the analyzer (Beckman Coulter Unicel DXI 800 Immunoassay, Brea, CA, USA). Statistical Package for the Social Sciences program (ver. 20.0, SPSS Inc., Chicago, IL) was used for statistical analyses. Distribution of variables was assessed with the Shapiro-Wilk test. Statistical comparisons were performed with the one-way analysis of variance (ANOVA) test (normally distributed data) and the Kruskal-Wallis test or the Mann Whitney-U test (skewed data). Appropriate post-hoc test was utilized for multiple comparisons between groups (Bonferroni and Dunn's). Chi-square test was utilized for categorical variables. The relationship between the maternal urinary and serum CA19-9 levels and other parameters were determined with the Spearman rho correlation coefficient. Normally distributed data are reported as mean  $\pm$  standard deviation, whereas skewed data are presented as median. All reported p values are two-tailed. Statistical significance was achieved when the p value was lower than 0.05.

## Results

Maternal age, gestational age and fetal gender were not statistically significantly different between groups (Table 1). Male fetuses constitute the majority in all groups (%70, %65, %65). Unilateral renal involvement was more frequent in both hydronephrosis groups (80% vs 65%). No statistically significant difference was found for maternal serum CA 19-9 levels between the groups. CA 19-9 level in maternal urine were elevated in both FH groups and this difference was statistically significant ( $p=0.014$ ) (Figure 1). Post-hoc Dunn's analysis revealed urinary CA19-9 levels were statistically significantly higher in severe FH group compared to the control group (Median = 75 vs 24; respectively,  $U = 8.6$ ,  $p = 0.014$ ). There was no significant difference between mild-moderate and severe FH groups ( $p = 0.189$ ).

To compare the possible diagnostic utility of urinary CA19-9 for FH, we combined two FH group ( $n = 40$ ) and compared with the control group ( $n = 20$ ) in terms of CA19-9 levels in urine. The Mann Whitney-U test indicated that urinary CA19-9 levels were significantly higher for the combined fetal hydronephrosis group than for the control group (Mean rank = 32.53 vs 21.95, respectively;  $U = 227$ ,  $p = 0.023$ ) (Figure 1). As seen in Table 2, the serum and urinary CA19-9 concentrations were positively and significantly correlated ( $r = 0.433$   $p = 0.001$ ). In addition, maternal mean serum and urinary CA19-9 levels were not found to be associated with maternal age, gestational age, gravidity or fetal gender.

## Discussion

Fetal renal obstruction can be transient or permanent and partial or complete. If the pathological process is in persistent nature, nephrogenic tissue may be affected resulting in cystic dysplasia. Therefore, differentiation of renal pathology is important in determining the outcome. Intuitively, FH may be considered as an obstructive pathology. However in some cases, FH can be the result of nonobstructive processes, such as vesicoureteral reflux or megaureter. However, the differentiation may not be possible until the delivery. Current diagnostic methods are not adequately predictive to differentiate postnatal clinically significant cases of FH, and in this circumstance, the antenatal management of this condition is challenging and controversial. Different serum and urine markers have been described in children to monitor hydronephrosis and its treatment, and utilization of such markers during the antenatal period may be promising in the detection of fetuses requiring treatment (13).

CA19-9 is an antigen of oncofetal origin, produced by amnion cells and decidua. Therefore, the concentration of this antigen in amniotic fluid is high and increases as the gestational period progress (6). Oncofetal antigens may pass from the embryoplacental compartment into the maternal circulation (14). The amount of antigen in maternal circulation depends on factors such as renal function, half-life, molecular weight and protein characteristics. Maternal serum level of CA 19-9 is increased throughout the pregnancy but does not exceed the normal values, hence CA 19-9 could be a useful marker during pregnancy (15). Maternal serum

CA19-9 levels were found to be significantly higher in primigravity, female fetus and fetal aneuploidy (16,17). In the current study, groups were homogenous and not significantly different in terms of gestational age, gravidity and fetal gender.

Inflammation and persistent obstruction in the kidney can lead to increased levels of CA 19-9 in circulation and urine (18,19). In line with studies indicating increased excretion of CA 19-9 in obstructive renal pathologies, it can be predicted that the CA19-9 concentration in amniotic fluid may be higher in cases of FH (10,11). Newborns diagnosed with a posterior urethral valve have been found to show elevated levels of CA 19-9 in urine samples taken immediately after birth and high levels were reported to be associated with a poor prognosis (20). Also, higher levels of CA 19-9 in amniotic fluid were reported in pregnancies with posterior urethral valves (21). In the light of this information, we aimed to evaluate maternal serum and urine CA 19-9 levels in pregnancies with FH.

In our study, there was a statistically significant difference between severe FH and control group in terms of urinary CA19-9 levels. Our finding was consistent with Kajbafzadeh et al. reported previously. They stated that CA 19-9 excretion increased significantly in urine of pregnant women with severe FH (22). Also in the current study, the pairwise analysis revealed an insignificant difference between mild-moderate FH and controls. We did not define a cut-off point for the diagnosis of severe FH because of the small number of cases and skewed distribution. Unspecified maternal renal disease or physiological renal changes due to pregnancy may be the factors affecting urinary excretion of CA19-9 that leads to outlier results and skewed distribution. When we compared the urinary CA 19-9 levels between controls and all fetal hydronephrosis cases (n = 40), the difference was still statistically significant. However, the skewed distribution of the data and insignificant difference between mild-moderate FH and controls make this marker useless to discriminate all FH cases. It was interesting that there was no statistically significant difference between groups for maternal serum CA 19-9 levels. Transplacental passage of CA 19-9 into maternal circulation has been described in previous studies (16,17,23). Our result may be due to the fact that even though a marked amount of the antigen was present in amniotic fluid it might be eliminated quickly in urine after transplacental passage. But, transplacental passage and ultimate maternal urinary excretion of CA 19-9 is intuitive since it has not been studied with in- or ex-vivo studies yet.

Last but not least, the difference in serum levels may fail to reach a statistically significant level due to the small sample size.

The strength of our study was that the homogeneity of the groups with regards to the maternal age, gravidity, fetal gender and gestational week at sampling. On the other hand, our investigation has several limitations. As a key limitation, the small number of cases in each group should be emphasized. Although mild FH is not a rare antenatal finding, severe and progressive cases are. In the unilateral FH cases, the diluting function of normal kidney can affect CA 19-9 levels. But due to the small sample size, we did not divide cases further. Another limitation of the study is that amniotic fluid levels of CA 19-9 were not evaluated. Furthermore, cases with progressive hydronephrosis requiring treatment were not identified because of a lack of neonatal outcomes. Also, it would be interesting to assess the correlation between increased maternal urinary CA19-9 level and neonatal urinary CA19-9 level.

Markedly elevated levels of CA19-9 in maternal urine can be detected in cases of severe FH. Our findings suggest that this noninvasive diagnostic method could detect clinically significant severe FH but the descriptive nature of the study prevents us from identifying a clinical significance of measuring maternal urinary CA19-9 level in FH. Also, many maternal subtle conditions affecting urinary excretion of CA 19-9 may result in high levels in urine and interfere with the diagnostic accuracy. Also, it should be kept in mind that CA19-9 is not expressed in 7% of people which limits the utility of the marker (24). Therefore, with the available data, we can not make precise comments about the use of CA 19-9 as a reliable diagnostic marker for FH. Further longitudinal and comprehensive studies are needed to identify the clinical significance of maternal urinary CA 19-9 level in the FH cases.

#### **Declaration of interest**

The authors report no conflicts of interest and have full control of the data.

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**Table 1:** Maternal clinical and biochemical characteristics of study groups.

	Mild-moderate FH n=20	Severe FH n=20	Control n=20	p
Maternal age (mean ±SD)	27.05±5.5	29.95±6.2	31.1±4.4	0.063 <sup>a</sup>
Gestational week(mean ±SD)	24.00±1.9	25.25±2.7	24.55±2.8	0.307 <sup>a</sup>
Gravidity (mean ±SD)	1.85±0.9	2.05±1.1	1.90±1.0	0.818 <sup>a</sup>
Fetal gender (F/M)	6/14	7/13	7/13	0.928 <sup>b</sup>
Affected kidney (B/U)	4/16	7/13	-	0.288 <sup>b</sup>
Serum CA19-9 (U/ml) (mean±SD)	14.4±11.6	19.4±12.3	16.9±8.0	0.353 <sup>a</sup>
(range)	5.0-34.0	2.4-38.0	6.0-31.1	
Urinary CA19-9 (U/ml) (median)	49.00 <sup>1,2</sup>	75.00 <sup>2</sup>	24.00 <sup>1</sup>	0.014 <sup>c*</sup>
(range)	1.6-241.0	20.1-485.0	1.0-357.0	

FH, fetal hydronephrosis; B,bilateral; F, female; M,male; SD, standart deviation; U,unilateral

<sup>a</sup> One-way analysis of variance test was used to compare continuous variables.

<sup>b</sup> Chi-square test was used to compare categorical variables.

<sup>c</sup> Kruskal–Wallis was used to compare continuous variables.

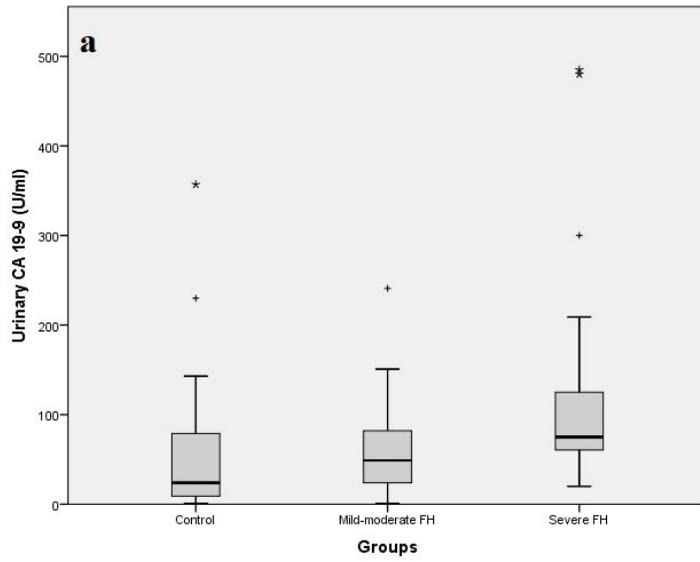
1,2 : Defined significance between each groups (1<2) (post-hoc test Dunn's)

\* Correlation is significant at the 0.05 level (2-tailed).

**Table 2:** Correlations between serum and urinary CA 19-9 levels and the other parameters.

	Serum CA19-9		Urinary CA19-9	
	r	p	r	p
Maternal age	-0.203	0.12	-0.205	0.125
Gestational age	-0.006	0.966	0.189	0.159
Gravidity	0.089	0.430	0.160	0.220
Fetal gender	-0.185	0.157	-0.077	0.569
Urinary CA19-9	0.433	0.001*	-	-

\* Correlation is significant at the 0.05 level (2-tailed).



+ Outlier cases  
\* Extreme cases

**Figure 1:** Urinary CA 19-9 levels between three groups (a). Urinary CA 19-9 levels between all FH group and controls (b). Distributions are compared with box plots graphs. FH: fetal hydronephrosis