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ORIGINAL PAPER

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Are changes in urinary parameters during pregnancy clinically significant?

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Abstract We aimed to objectively determine changes in the various urinary parameters along with CaOx saturation level during pregnancy. The study included 15 pregnant women who had no known diseases and were taking no medication except prenatal supplements. Mean age of the patients was 26 years (range 20–30). In all of them, this study was carried out in each trimester and 3 months post partum. All participants were followed up, and blood and urine samples were obtained during the pregnancy and during 3 months post partum. All subjects collected 24-h urine samples. The pregnant women had hypercalciuria in all three trimesters. Except for the first trimester, urine calcium levels in all trimesters were significantly higher when compared with the post-partum period ($P < 0.01$ for second trimester, $P < 0.05$ for third trimester). Urine oxalate level in post-partum period was significantly higher than urine oxalate levels in each trimester ($P < 0.05$). The urine citrate levels were similarly higher than normal levels in three trimesters. Urine citrate level of the post-partum period was in normal reference ranges. This difference was not stastistically significant ($P > 0.05$). We believe that hypercalciuria encountered at pregnancy is a reversible physiologic condition. Also, citrate and magnesium as urinary inhibitors increased in urine during gestation preventing stone formation. We think that long time periods are needed for hypercalciuria to be able to lead to the formation of urinary calculi in pregnant women (except women having a positive family history). Therefore, we think that the pregnancy alone does not predispose to a suitable condition for calculi.

Keywords Pregnancy · Hypercalciuria · Inhibitors of stone formation

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Introduction

The occurrence of urinary tract calculi in a pregnant woman is one of the most problematic conditions. Metabolic effects during pregnancy such as hyperuricuria and hypercalciuria, changes in inhibitors of lithiasis formation, stasis, relative dehydratation, and the presence of infection all have an impact on stone formation. A normal pregnancy causes hypercalciuria. It is suggested that hypercalciuria leads to crystalluria and urolithiasis, but hypercalciuria depending on pregnancy is an exception to the rule [1–3]. We investigated through a prospective study whether pregnancy had an increasing or decreasing effect on inhibitors of lithiasis formation in urine. We also wanted to detect the levels of crystals in the urine of pregnant women, which may contribute to stone formation.

Subjects and methods

The goal of this study was to objectively assess levels of calcium, oxalate, uric acid, sodium, magnesium, and citrate excreted in 24-h urine samples of pregnant women.

Twenty-five pregnant women, who had no known diseases and who were taking no medication except prenatal supplements, were enrolled in the study. Ten

participants were excluded for not following up with the regular protocol. The study was completed with 15 pregnant women. Their ages ranged from 20 to 30 years (mean age 26 years). In all of them, this study was carried out in each trimester and 3 months post partum. Pregnant women took uncontrolled diets during pregnancy.

The institutional ethical committee approved this study, and all participants read and signed an informed consent form.

Study during pregnancy

All participants were followed up during the pregnancy and during 3 months post partum. During this period, the patients were asked whether they experienced an acute episode of ureteral colic or not. All of them were evaluated during the pregnancy and at 3 months post-partum by urinary ultrasonography to ascertain the presence of stone or hydronephrosis. All pregnant women delivered via caesarean section. All babies had a normal general status and were alive.

Blood and urine samples were obtained at the end of each trimester of pregnancy (at the 12th, 24th, and 38th weeks) and at 3 months post partum. All subjects collected 24-h urine samples, and the samples of fasting blood were taken at the end of the collection period in the morning.

The urine collection method was as follows [4–6]:

1. One 16-h urine sample and one 8-h urine sample were collected.
2. Sample 1 was collected between 0800 and 2400 in a bottle containing 10–20 ml of 6 mol/l HCl.
3. Sample 2 was collected between 2400 and 0800 in a bottle containing 10 ml of 0.3 mol/l sodium azide.

Hydrochloric acid is used to prevent precipitation of calcium phosphate and calcium oxalate, and counteracts oxidation of ascorbate to oxalate. Analysis of urate can be carried out in collections with sodium azide but in samples with HCl only following alkalinization with sodium hydroxide.

Measurements

Blood urea nitrogen, creatinine, sodium, potassium, inorganic phosphorus, calcium, uric acid, and magnesium were measured by autoanalyser (Dade Behring Inc., New York, USA), citrate by enzymatic bioanalysis using citrate lyase (Boehringer Mannheim/ R-Biopharm, Darmstadt, Germany), and oxalate by enzymatic determination (Sigma Diagnostics, St Louis, USA). Urine pH was measured by a strip method (Roche Diagnostic, Mannheim, Germany) and checked with a pH meter (Beckman 071, Beckman Instruments, Fullerton, California, USA).

Sodium, potassium, uric acid, calcium, and creatinine were measured in blood and urine. Oxalate, citrate, urate, magnesium, creatinine, urea, calcium, and pH together with volume were examined only in urine.

The excretion of more than 200 mg of calcium in 24-h urine or the excretion of more than 6 mmol/l in women was accepted as ''hypercalciuria'' [6–9]. The statistical analysis was made according to both cut-off points.

The ion-activity product of calcium oxalate [AP (CaOx)] index was calculated according to the formula [6, 10]:

$$\mathrm{AP(CaOx)index} = \frac{1.9\mathrm{Ca}^{0.84}\mathrm{Ox}}{\mathrm{Cit}^{0.22}\mathrm{Mg}^{0.12}\mathrm{V}^{1.03}}.$$

Also, the levels of 24-h urine chemistries were indexed to urinary creatinine for pregnant women according to periods of pregnancy [6].

All data were expressed as mean and standard deviation. Non-parametric statistical methods were applied to continuous variables. Values for serum and urine chemistries in three trimesters were compared using Friedman's test followed by post hoc Wilcoxon signed rank test. Post-partum serum and urine values were compared with values of each trimester using the Wilcoxon signed-rank test. To monitor the possible confounding effect of body weight on urine calcium levels, we used a ratio calculated by dividing urine calcium of each subject to her body weight. A P value less than 0.05 was accepted as significant. Statistical analyses were performed using SPSS 9.0 for Windows (SPSS Inc., Chicago, IL).

Results

The group included both primiparous and multiparous women [gravidity 1–4 (mean 1.8), parity 0–2 (mean 0.6)]. None of the patients reported any history of urolithiasis. In 12 of the 15 (80%) pregnant women, hydroureteronephrosis occurred during the second and third trimesters. There were no correlations between the presence of hydronephrosis and urinary parameters ($P > 0.05$).

Twenty-four-hour urine parameters, which are indexed to urinary creatinine by each period, are shown in Table 1 and all comparisons were made by using these values. The results for serum and 24-h urine parameters for each period are shown in Table 2. Serum parameters were in the normal ranges in all the four periods. Creatinine clearance was higher than the normal in the first and second trimesters, and it dropped to a normal level in the post-partum period. It was in the normal range in the third trimester and post-partum period. We compared creatinine clearances in each trimester and in the post-partum period. Mean urinary levels of calcium were above the normal range in three trimesters according to both hypercalciuria definitions (< 6.0 mmol/24 h for women) [6–9]. However, urine calcium levels in the

Table 1 Values of serum and 24-h urine chemistries (indexed to urinary creatinine) for pregnant women according to periods of pregnancy (mean ± SD)

	First	Second	Third	Post partum
Serum				
BUN (mg/dl)	7.6 ± 1.68	7.3 ± 2.13	8.0 ± 2.40	10.2 ± 2.84
Creatinine (mg/dl)	0.7 ± 0.12	0.5 ± 0.06	0.6 ± 0.12	1.2 ± 1.88
Sodium (mEq/l)	138 ± 0.40	136 ± 0.35	137 ± 0.5	139 ± 0.4
Calcium (mg/dl)	8.6 ± 0.35	8.7 ± 0.51	8.9 ± 0.41	9.3 ± 0.48
Uric acid (mg/dl)	3.0 ± 0.81	2.9 ± 0.73	3.4 ± 0.78	4.2 ± 1.03
Potassium (mEq/l)	4.1 ± 0.31	4.1 ± 0.37	4.2 ± 0.32	4.4 ± 1.55
Urine				
Calcium (mmol/g) creatinine	0.68 ± 0.30	1.16 ± 0.96	0.87 ± 0.69	0.51 ± 0.51*, **
Oxalate (mmol/g) creatinine	0.01 ± 0.007	0.03 ± 0.05	0.03 ± 0.05	0.14 ± 0.33*
Phosphorus (mmol/g) creatinine	2.03 ± 0.57	2.93 ± 1.99	2.15 ± 1.49	3.26 ± 2.75
Uric acid (mmol/g) creatinine	0.37 ± 0.06	0.62 ± 0.50	0.42 ± 0.28	0.54 ± 0.62
Citrate (mmol/g) creatinine	0.06 ± 0.02	0.10 ± 0.10	0.09 ± 0.15	0.18 ± 0.37
Magnesium (mmol/g) creatinine	0.56 ± 0.23	0.81 ± 0.56	0.73 ± 0.77	0.71 ± 0.72

*$P < 0.05$; **$P < 0.01$ (P values indicate the statistical significance of the changes in the urine parameters measured in between post-partum period and in each trimesters)

Table 2 Values of 24-h urine chemistries (mmol) for pregnant women according to periods of pregnancy (mean ± SD)

Urine	First	Second	Third	Post partum
Volume (ml/day)	1,463 ± 898.52	1,568 ± 895.22	1,199 ± 654.13	1,534 ± 1,220.87
Calcium (mmol/24 h)	6.6 ± 4.0	8.0 ± 5.56	6.3 ± 4.47	3.3 ± 2.29
Oxalate (mmol/24 h)	0.10 ± 0.05	0.20 ± 0.23	0.14 ± 0.16	0.42 ± 0.58
AP(CaOx) index	2.29 ± 1.90	2.93 ± 2.46	2.54 ± 1.75	3.12 ± 2.44
Calcium (mmol/l/kg)	3.79 ± 1.97	3.71 ± 2.05	3.46 ± 1.85	2.08 ± 1.70
Creatinine clearance	104.55 ± 41.16	133.05 ± 74.21	92.23 ± 43.03	126 ± 59.07
Phosphorus (mmol/24 h)	19.08 ± 8.45	21.71 ± 11.51	17.51 ± 10.85	21.17 ± 8.05
Uric acid (mmol/24 h)	3.59 ± 1.60	4.43 ± 2.59	3.20 ± 1.56	3.18 ± 1.07
Citrate (mmol/24 h)	0.55 ± 0.26	0.62 ± 0.53	0.54 ± 0.51	0.63 ± 0.60
Magnesium (mmol/24 h)	5.35 ± 3.18	5.76 ± 3.31	5.34 ± 3.88	4.64 ± 1.29
pH	5.70 ± 1.06	6.16 ± 0.74	6.03 ± 0.81	5.66 ± 1.04

C_{cr} creatinine clearance in l/24 h, mg/C_{cr} mg/l creatinine clearance

post-partum period were in the normal range. Urine calcium levels were statistically similar in all the three trimesters ($P > 0.05$). Except for the first trimester, urine calcium levels in all trimesters were significantly higher when compared with that of the post-partum period ($P < 0.01$ for second trimester, $P < 0.05$ for third trimester). The numbers of pregnant women with hypercalciuria in each period are shown in Table 3. Afterwards, the same comparison was done in terms of the levels of urinary calcium excretion corrected by the body weight. Urine calcium excretion was established as (mmol/l/kg). It was shown that these differences regarding the urinary calcium levels continued, but the significance was lower ($P < 0.05$).

Urine oxalate levels in all three trimesters were similar ($P < 0.05$). However, urine oxalate levels in all three trimesters were in the normal range but above normal in the post-partum period (< 0.4 mmol/24 h for women) [6]. Additionally, urine oxalate levels in the post-partum period were significantly higher than the urine oxalate levels in each trimester ($P < 0.05$). However, AP(CaOx) index values did not differ significantly during pregnancy and the post-partum period. In all periods, AP(CaOx) index values were above the normal ranges (< 1.3 for women) [6].

The urine uric acid levels were similar and above normal in all four periods (< 2.36/24 h for women).

The urine citrate levels were higher than the normal in all four periods (> 0.46 mmol/24 h for women). We then compared urine citrate levels in each trimester and the urine citrate level in the post-partum period. The results were not significantly different ($P > 0.05$).

The urine magnesium levels were similar and normal in the four periods (> 3 mmol for women). There was no statistical difference among the results.

The urine phosphorus levels were similar and normal in the four periods (< 35 mmol/24 h for women). There was no significant difference among the results ($P < 0.05$).

The urine sodium and potassium levels were similar and did not differ in all four trimesters ($P > 0.05$).

Mean urine pH values were similar and did not differ in the first and third trimesters from the post-partum period. Urine pH values in the second trimester were significantly higher than the urine sodium level in the post-partum period ($P < 0.05$).

Although, the total serum calcium levels were also similar and at normal levels in the four periods, the total

Table 3 Numbers of pregnant women with hypercalciuria in each period

Patients	First trimester	Second trimester	Third trimester	Post partum
Hypercalciuric	7 (46.6%)	9 (60%)	8 (53.4%)	8 (53.4%)
Normal	8 (53.4%)	6 (40%)	7 (46.6%)	7 (46.6%)
Total	15 (100%)	15 (100%)	15 (100%)	15 (100%)

serum calcium level decreased throughout pregnancy and increased in the post-partum period.

Discussion

Symptomatic urolithiasis in pregnancy is a rare condition. However, pain resulting from urinary calculi requires hospitalization during the pregnancy [1, 11, 12]. The incidence of urinary tract calculi in pregnant women is reported to be between 1:1,500 and 1:2,500 [1, 2, 13–16]. Most pregnant women with urolithiasis are present in the second or third trimester [13, 17, 18]. The frequency, principal causes, and type of stone occurring during pregnancy are similar to those in non-pregnant women [11, 18, 19]. About 75% of urinary tract stones occurring during pregnancy are calcium stones, 10–20% of stones are uric acid stones and about 1% are cystine stones. Struvite calculi occur during pregnancy in about the same frequency as in non-pregnant women.

Anatomic and metabolic changes in pregnancy may play an important role in stone formation. Anatomic changes that occur in the pregnant woman during pregnancy affect the formation of stone. Physiologic hydroureteronephrosis is seen in 90% of pregnant women [1, 2, 11]. This dilatation is usually asymptomatic, but it can rarely cause acute pain. In our study, we found that hydroureteronephrosis in 12 of the 15 (80%) pregnant women and patients neither experienced ureteral colic episodes nor had urolithiasis during the study.

Metabolic effects during pregnancy such as hypercalciuria and hyperuricuria, changes in inhibitors of lithiasis formation, stasis, relative dehydratation, and the presence of infection all have an impact on stone formation. Most pregnant women have absorptive hypercalciuria and hyperuricuria [1, 20]. Hypercalciuria is the result of elevation of 1,25-dihydroxyvitamin D. The circulating level of 1,25-dihydroxyvitamin D increases as a consequence of fetal needs for calcium. The developing fetus takes its calcium requirement from the mother. The access of calcium across the placenta would lower the maternal ionized calcium concentration and induce secondary hyperparathyroidism, which leads to increased 1,25-dihydroxyvitamin D production. Intestinal calcium absorption is regulated by means of 1,25-dihydroxyvitamin D hormone. Thus, the increase in intestinal absorption and bone mobilization of calcium leads to hypercalciuria [1, 12, 20, 21]. In our study, we observed hypercalciuria in all pregnant women in all three trimesters. At third month post partum, hypercalciuria resolved and returned to normal levels in all participants. Although, Gertner et al. [20] showed a significant correlation between their results for calcium excretion during three trimesters and calcium supplementation during pregnancy, it is not known whether calcium supplementation during pregnancy bears a risk of stone formation in pregnant women. Howarth et al. [22] reported that the levels of calcium excretion in pregnant women were higher than in women who had calcium-oxalate nephrolithiasis.

The risk factors for uric acid stone formation include low urine volume and acid urine [12]. In our study, we established hyperuricuria in all four periods (Table 2). Our patients had slightly acidic urine pH values and adequate urine volumes.

We did not observe high urine oxalate levels in any of the pregnant women. High urine oxalate levels were observed only in the post-partum period. We think that some foods rich in oxalate, such as grape molasses, given to the mother with the aim of increasing mother milk, could cause this result.

Despite the levels of urinary inhibitors such as citrate, magnesium also increased in urine during gestation [23–25]. As a result, the incidence and predisposing factors of urinary tract stones are generally the same as in non-pregnant women.

In order for a stone to form in the urinary tract, crystals should be found, be retained, aggregate, and grow. Crystal formation occurs as a result of an imbalance in physiochemical factors in the urine. Normal urine is supersaturated for calcium-oxalate crystal formation, but crystals fail to form because of the inhibitory characteristics of normal urine [11, 12]. The citrate and magnesium, which are inhibitors of calcium stone formation increase during pregnancy and probably prevent stone formation [16, 24]. Urinary citrate is an important substance for crystallization of calcium oxalate and calcium phosphate and inhibits the growth of these crystals. It is well recognized that women are less prone than men to develop calcium stones, because they usually excrete more citrate than men [25]. It is not known what causes the higher citrate excretion in women. However, it has been suggested to be due to the female sex steroids [1, 25]. Additionally, sex differences in diet and life style may contribute to the excretion of promoters [26].

In the present study, the citrate increased slightly in the urine of pregnant women in all four periods. The magnesium, as other urinary inhibitors, was similar and normal in all four periods.

Pregnancy may be affected by several physiologic adaptations. The glomerular filtration rate increases by 25–50% during pregnancy [1, 20]. Excretions of sodium, calcium, and uric acid are increased. We saw that creatinine clearance was above normal levels during pregnancy. It returned to the normal level in the post-partum period. We also found that urine uric acid levels were above normal, and urine sodium levels were higher than the normal in all four periods. Howarth et al. [22] suggested that the increased calcium excretion during pregnancy was related to the increased filtered load of calcium secondary to the increased glomerular filtration rate.

The increased calcium excretion during pregnancy increases the risk for calcium stone formation, but the increased excretion of crystal inhibitors that occurs during gestation balances this risk. Our group included

both primiparous and multiparous women [gravidity 1–4 (mean 1.8), parity 0–2 (mean 0.6)]. The time period to be exposed to hypercalciuria was short since the delivery number was low.

In the present study, AP(CaOx) index values calculated for three trimesters and the post-partum period did not differ significantly. Thus, we believe that the hypercalciuria encountered during pregnancy is a reversible physiologic condition, and this alone may not reflect the stone formation risk. Also, citrate and magnesium as urinary inhibitors increased in urine during gestation to prevent stone formation. The functions of the body are reverted to the normal state in the post-partum period. Therefore, we think that pregnancy alone does not predispose to a suitable condition for calculi. We believe that long time periods are needed for hypercalciuria to be able to lead to the formation of urinary calculus in pregnant women (except women having a positive family history). Further studies are needed to determine whether women who have had many pregnancies and therefore have been exposed to hypercalciuria for a longer period of time have a higher risk for urinary tract stone formation than women who have been pregnant only once or twice.

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