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The Deleterious Effect of Inappropriate Calcium and Vitamin D Supplementation during Pregnancy in Women Predisposed to Calcium Oxalate Urolithiasis

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Abstract

Background: Gestational formation of new urolithiasis is rare yet the impact of inappropriate gestational calcium and vitamin D supplementation (Ca/DS) is underestimated. **Patients and Methods**: we retrospectively evaluated 75 pregnant women with history of UL, yet were stable for >2 years on dietary restrictions, for new UL after Ca/DS. **Results:** During the past 5 years 21 (48%) of those who had received Ca/DS had developed UL and all had high Vitamin D with hypercalcemia while the remaining 31 patients, without Ca/DS, did not have UL and maintained normal vitamin D urinary calcium without need for supplementation. Overt UL was evident by 30th weeks of gestations and most were diagnosed by ultrasonography and managed by medical expulsive therapy. **Conclusion**: in patients with history of UL, prudent use of Ca/DS is indicated to avoid new UL.

Keywords

Calcium, Kidney, Pregnancy, Stones, Urolithiasis, Vitamin D

1. Introduction

Globally, between 1% and 15% of people are affected by urolithiasis (UL) at some point in their lives culminating in an incidence of 1394:100,000 [1]. In 2005, its global health care had reached $5.3 billion per year in the United States alone [2]. Moreover, in 2015, 22.1 million cases occurred, resulting in about 16,100 deaths [3]. In women, a 2014 review of two decades of data from a ter-

tiary hospital revealed significant increase in the general incidence of UL yet not in pregnant patients [4]. Though variable, the estimated incidence of symptomatic ones rarely exceeds 1 in 3300 pregnancies [5]. Such low incidence, of UL during pregnancy, has been attributed to, 1) increase glomerular filtration rate, 2) augmented excretion of UL inhibitors, such as citrate, magnesium, and glycosaminoglycans (nephrocalcin) that inhibits oxalate stone formation, and 3) alkalinization of urine due to increased citrate excretion that protects against urinary uric acid supersaturation [6]. For normal pregnancy, the need for additional supplement of folic acid and iron is well established. On the other hand, calcium and/or vitamin D supplementation (Ca/DS) has been promoted as essential supplements since Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal bone mineralization. Moreover, its extra-skeletal role include, reduction of inflammation as well as modulation of such processes as cell growth, neuromuscular and immune function, and glucose metabolism [7]. Unfortunately, the impact of such supplementation on hypercalciuria and subsequent UL is underestimated in women susceptible to UL. Hence, we conducted this study to assess the role of inappropriate Ca/DS in this patient population.

2. Patients and Methods

The study was conducted at Amiri renal center in Kuwait City. The center is a referral institution for patients with renal disease in the 2 major hospitals in Kuwait City and is a tertiary care unit for the other hospitals in Kuwait.

2.1. Study Design

We retrospectively analyzed our medical records, between 1st January 2018 till 31st December 2022, on pregnant women, who had history of UL yet without recurrence for >2 years prior to conception while on dietary stone-prophylaxis (vide infera). Analysis included, 1) history of intake of Ca/DS, 2) new UL, 3) methods of diagnosis of new UL, 4) patient's demographical data (age, duration of UL and duration of conception at diagnosis), 5) serum levels of parathyroid hormone and 1,25 Vitamin D and 6) 24-hour urinary levels of calcium, phosphorus, uric acid, magnesium, citrate, oxalate and cysteine.

2.2. Dietary Stone-Prophylaxis

The latter entailed: 1) low salt, red-meat and green leafy vegetable, 2) moderate amounts of milk, dairy products, poultry and certain fish-items yet without Ca/DS, and 3) high water intake (≥2 liters/day) [8].

2.3. Exclusion Criteria

Patients were excluded if they had, 1) significant stone load or staghorn calculi, 2) struvite stones (infected with urea-splitting bacteria), 3) cystine stones, 4) congenital anomalies of the collecting system, 5) underlying renal disease (GFR

≤ 60 ml/minute), 6) severe primary or secondary osteoporosis that indicates requiring Ca/DS, and 7) history of non-compliance with previous dietary restrictions.

2.4. Statistical Analysis

SPSS statistical package version 26 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since demographical data, serum levels of parathyroid hormone, 1,25 Vitamin D and 24-hour urinary levels of serum levels of parathyroid hormone and 1,25 Vitamin D were normally distributed, they were expressed as Mean ± SD and their comparison was done using t-test.

3. Results

In the past 5 years, a total of 77 pregnant women fulfilled the criteria and hence were analyzed. Two patients did not have adequate biochemical data and were excluded. Hence, the study population included 75 patients. According to new UL and intake of Ca/DS they were divided into 3 groups. Group 1, included 21 patients who had received Ca/DS and had developed new UL during the study. Group 2, included 23 patients who had received Ca/DS yet did not have new UL. Group 3, included 31 patients who did not receive Ca/D and did not have new UL.

3.1. Group Comparison

The demographical data and biochemical measurements, of those patients' groups, are summarized in (Table 1). The 3 groups had similar demographical characteristics and normal biochemical measurement except for high levels of Vitamin D and urinary calcium levels in group 1 and 2 ($p < 0.00001$).

3.2. Diagnosis of New UL

In group 1, 19 patients presented with typical renal colic and 2 with asymptomatic microscopic hematuria. Diagnosis of UL was established by ultrasonography revealing kidney stones and/or hydronephrosis. In 2 patients who presented in the 3rd trimester, failure of ultrasonography indicated low-dose CT to confirm diagnosis of UL and rule out other etiologies.

3.3. Management

Ca/DS was discontinued after diagnosis of UL and/or hypercalcemia in group 1 and 2 patients. Those in group 1, had received conservative expulsive therapy with Intravenous hydration, analgesia, bed rest and antiemetics that resulted in spontaneous passage of stones in most patients. Only 2 patients had endoscopic placement of temporary double J stent placement for severe obstruction in the 3rd trimester followed by postpartum endoscopic lithotripsy. None of the patients had, 1) received alpha adrenergic blocking agents or 2) associated infection or significant kidney damage.

Table 1. Demographical data and metabolic changes in the 3 groups of stone formers.

	Study groups *			
	Group 1	Group 2	Group 3	
	(n = 21)	(n = 23)	(n = 31)	
Character:				
Age: (years)	26 ± 4	27 ± 4	27 ± 5	
Prior nephrolithiasis: (months)	41 ± 11	41 ± 13	43 ± 12	
Duration of conception: (months)	30 ± 4	30 ± 5	30 ± 3	
Metabolic changes:				Normal range**
A-Serum:				
Parathyroid hormone:	31 ± 6	31 ± 5	39 ± 8	14 - 65
1,25 Vitamin D:	319 ± 43	309 ± 35	166 ± 41	75 - 250
B-24-h urine measurements:				
Calcium:	8 ± 0	8 ± 0	7 ± 1	2.5 - 7.5
Phosphorus:	30 ± 3	31 ± 4	31 ± 2	12 - 42
Uric acid:	4 ± 2	4 ± 0	4 ± 1	1.5 - 4.4
Magnesium:	4 ± 0	4 ± 1	4 ± 0	3 - 5
Citrate:	1095 ± 63	1093 ± 61	1068 ± 79	228 - 1191
Oxalate:	0.4 ± 0	0.4 ± 0	0.3 ± 0	0.1 - 0.5
Cystine:	32 ± 8	32 ± 7	35 ± 8	28 - 290

*Group 1: pregnant with Ca/vit D supplementation and formed stones, Group 2: pregnant with Ca/vit D supplementation yet no stones, group 3: pregnant yet no Ca/vit D supplementation & no stones. **Measurements: parathyroid hormone: pg/ml, vitamin D: nmol/L, calcium + phosphorus + uric acid + Magnesium +citrate: mmol/L & oxalats: umol/L. Statistical analysis: $P < 0.00001$ in levels of (parathyroid hormone, vitamin D and urinary calcium) between group 3 and the other 2 groups. No significant difference between demographical data and other 25-hour urine measurements between groups.

3.4. Follow Up

After discontinuation of Ca/DS, all patients in group 1 and 2 had normal biochemical tests within 2 weeks. A total of 13 subsequent conceptions were recorded without new UL of whom 3 as a 3rd conception.

4. Discussion

At start, all selected patients had ≥2 years stable UL disorder without new stone formation as well as normal serum and urinary electrolytes especially for calcium, citrate, oxalate and cystine. Moreover, pregnant women without Ca/DS had normal biochemical parameters indicating adequate levels of calcium, vitamin D and parathyroid hormone consistent with previous reports indicating adequate maternal adaptation to fetal and neonatal needs of Ca/VD [9]. Such adaptation was attributed to, 1) increase intestinal absorption of Ca that doubles after 12 weeks in gestation due to placental activation of 1,25 dihydroxy vitamin D with maternal skeleton-storage for the peak fetal demand for calcium in the third trimester, 2) lactational resorption of maternal skeleton via osteoclast acti-

vation to provide Ca of breast milk and 3) pseudohypoparathyroidism mediated by parathyroid hormone-related protein, produced in the breasts or placenta during pregnancy, and by the breasts alone during lactation. Moreover, such changes are, 1) not suppressed by higher intake of Ca, and 2) do not affect bone volume which is restored shortly after weaning [9]. Hence, inappropriate Ca/DS can lead to hypercalciuria which is a major risk factor for UL in susceptible patients. In our study, such deleterious effect was evident in women treated with Ca/DS (group 1 & 2) compared to those in group 3. Moreover, significant stone-load was evident within a short period of 30 weeks and in 21(48%) of the exposed women. In our patients, overt renal colic was the most common presentation of new UL (91%) with microscopic hematuria in the rest. Such finding indicates periodic urine testing in such patients. Historically, inferior results were associated with the use of ultrasonography, in diagnosis of UL during pregnancy, with sensitivity, specificity, and accuracy as 40%, 84%, and 53%, respectively [10]. In our study, such safe and practical examination confirmed diagnosis in 91% of cases. Only 2 patients had to be subjected to low-dose CT (radiation exposure of less than 50 mGy) to confirm UL diagnosis and rule others which is considered safe at the 3rd trimester by American College of Obstetricians and Gynecologists. [11]. Moreover, ureteroscopy was used to place temporary DJS followed by postpartum endoscopic lithotripsy in 2 patients [12]. In agreement with previous reports, the timing of overt gestational UL is 30 weeks [13]. Hence, in such patient population, vigilant follow up may detect early UL and hence, limits its subsequent major complications and interventions. As seen in our study, conservative expulsive therapy was adequate [14]. In our patients, alpha adrenergic blocking agents were not used since not approved by the U.S. Food and Drug Administration for use during pregnancy [15]. Moreover, pain-management indicated, 1) limited use of narcotics (Morphine sulfate and Meperidine) if Hyoscine butylbromide and Acetaminophen fail, and 2) early placement of DJS to relive pain and obstruction. Our early diagnosis and management were to avoid, 1) long-term use of narcotics known to be associated fetal narcotic addiction, intrauterine growth retardation and premature labor, 2) Codeine for its association with fetal defects and 3) Non-steroidal anti-inflammatory drug that are associated with increased risk of miscarriage when used in the first trimester, fetal renal anomalies, fetal pulmonary hypertension, and premature closure of the ductus arteriosus at term [16]. UL, during pregnancy, is a serious disorder with, 1) difficult diagnosis that mimics acute cholecystitis, diverticulitis, pancreatitis, urinary tract infection or complications of pregnancy viz. preterm labor, ectopic pregnancy, abruptio placentae, 2) limited diagnostic and management options, and 3) high health risk to mother and fetus due to urinary tract infections, kidney loss and interventional complications [17]. Hence, prevention, early diagnosis and management is indicated.

5. Conclusion

In conclusion, prudent use of Ca/DS, during pregnancy, is essential to avoid UL.

Statement of Ethics

The case was reported according to World Medical Association Declaration of Helsinki; There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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