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Association of serum vitamin D levels and urinary tract infection in pregnant women: A case control study

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ABSTRACT

Objective: Urinary tract infection (UTI) is common during pregnancy and can cause serious complications for the mother and fetus. Vitamin D, is known to have an effect on the urothelium, with immunomodulatory capacity against bacterial infection. This study explored the association between serum vitamin D levels and urinary tract infections in pregnant women.

Study design: In this case control study, 187 participants including, 97 pregnant women diagnosed as a symptomatic UTI (case group) and 90 matched healthy pregnant women (control group) were consecutively enrolled from prenatal care clinic of Imam Reza Hospital in Urmia, North West of Iran. The two groups were matched for trimester and parity, and sexual intercourse. Blood samples were collected from both groups. Chemiluminescent immunoassay (CLIA) was used to evaluate the serum vitamin D levels. We used a binary multivariate unconditional logistic regression approach to evaluate the association between UTI and vitamin D and risk factor of the UTI.

Results: Vitamin D deficiency (less than 20 ng/mL) was diagnosed in 85.7% of case group and 52.2% of control group. The serum vitamin D levels were significantly lower in pregnant women in the case group compared to the control group (12.7 ± 5.9 ng/ml vs 26.05 ± 10.37; $p < 0.001$). Pregnant women in case group with acute pyelonephritis had significantly lower serum vitamin D levels than those with Cystitis ($p < 0.05$). The serum vitamin D level of less than 20 ng/ml was the only factor associated with UTI after adjusting for all the confounders in multiple binary logistic regression modeling (AdjOR = 3.67; 95% of CI: 1.19–6.24; $p < 0.001$).

Conclusions: Women with vitamin D deficiencies are at increased risk of urinary tract infections during pregnancy. However, further studies are essential to confirm these observed results.

Introduction

Urinary tract infection (UTI) is a common infection during pregnancy in response to physiological changes in the urinary tract during pregnancy, hormonal influences, urinary tract obstruction by the uterus and increased vesicoureteral reflux [1]. Acute cystitis occurs in 1%–2% of pregnant women and the estimated incidence of acute pyelonephritis during pregnancy is 0.5%–2% [2]. Urinary tract infection in pregnancy can have serious complications affecting the health of both mother and fetus, such as preterm labor, low birth weight, intrauterine growth retardation, fetal death, or maternal systemic infection [3,4]. Risk factors well known related to bacteriuria in pregnancy included; previous UTI, anatomic urinary tract abnormalities, functional urinary tract abnormalities, diabetes mellitus, sickle cell disease, low socioeconomic status, multiparity, increased frequency of sexual activity [4,5]. The asymptomatic bacteriuria which occurs in 1.9–15% of pregnant women and is a major risk factor for symptomatic UTIs during pregnancy [6].

Vitamin D is essential for human health, and is an important hormone during pregnancy. Vitamin D may come both from dietary sources and from synthesis in the skin triggered by sun

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exposure [7]. UVB[1] sunlight exposure, rather than diet, has been reported as the main source [8]. Vitamin D deficiency is now recognized as a pandemic [9]. During pregnancy, vitamin D deficiency or insufficiency may develop [10]. There is evidence of an association between a low maternal vitamin D status and a high risk of adverse pregnancy outcomes [11]. Moreover there are in-vitro evidence, that vitamin D deficiency predisposes the urinary tract to failure to produce bactericidal antimicrobial peptides such as human Cathelicidin and β-defensines during infection and also increases the severity of the disease [12,13]. Endogenous antimicrobial peptides (AMPs) such as Cathelicidin (LL-37) and human β-defensines are important components of the innate defense in the urinary tract [12,14,15]. Cathelicidin is secreted into the bloodstream by immune cells and at the epithelial surfaces of all multicellular organisms and has a protective role against infection [15–17]. The antimicrobial peptide Cathelicidin increases cytokines, stimulates macrophage proliferation and up regulates the vitamin D receptor expressed on macrophages [18]. β-defensins are widely expressed throughout our epithelia and increased in kidney infection, and attract white cells [12,19,20].

Vitamin D deficiency has been linked with infectious diseases, such as sepsis [21], tuberculosis [22], and inflammatory bowel disease [23]. Our previous observational studies showed that vitamin D deficiency may be associated with UTI in children and menopausal women [24–26], yet no studies have explored the possibility of an association between serum vitamin D levels and UTI in pregnant women. The associations between birth defects and some antibiotics in pregnancy are unclear; however, there exists a rapidly growing problem of resistance to common UTI antibiotics [27]. More importantly, the prevention of UTI can improve maternal and infant health and reduce the risk of preterm birth. The prevention of UTI in pregnancy is the essential component of prenatal care and it is one of the main recommendations of 'The Review on Global Antimicrobial Resistance' (2016) [28,29]. In fact, we hypothesize that a lack of Cathelicidin and β-defensines caused by vitamin D deficiency could impair the immunological response and increase the predisposition to UTI. This study compared the serum vitamin D levels in pregnant women with UTIs and of healthy pregnant women.

Materials and methods

Study sites

Between February to July in 2018, a case-control study was conducted at a prenatal care clinic of a public hospital (Imam Reza Hospital) in Urmia, North west of Iran. Participants were recruited from pregnant women who sought care from the prenatal care clinics for UTI symptoms, and routine prenatal care.

Study design and selection of cases and controls

This case-control study investigated the association between serum vitamin D levels and UTI in 187 pregnant women. In this study, 97 pregnant women diagnosed as symptomatic UTI (case group) were compared with 90 healthy pregnant women (control group) who had neither symptomatic nor asymptomatic bacteriuria. The inclusion criteria were the age range of 18–35 years not having recently received antibiotics or vitamin D supplementation. The exclusion criteria [4] for both groups were: a history of recurrent UTI, urinary tract anomalies, anemia, obesity (BMI 30 $\geq$ kg/m^2), diabetes, urinary tract stent, urinary incontinence, neurogenic bladder, asymptomatic bacteriuria, kidney stones, or substance abuse and immune system inhibitory drugs. Efforts were made to frequency match the cases and controls by parity, first (6–14 week), second (15–28 week), third (29–42 week) trimesters of pregnancy, and frequency of sexual intercourse [4]. The group matching was performed, selecting 90 healthy pregnant women (control group) who met the inclusion criteria and were presented in the prenatal care clinic. Those who met the inclusion criteria were recruited until the calculated sample size was attained.

Data collection

All participants were informed about the purpose of the study and were invited to take part in the study. The women who agreed and signed the informed consent, participated in the study. Data were collected in the prenatal care clinic using a self-administered questionnaire. The questionnaire included; demographic characteristics, an obstetrical questionnaire and the frequency of sexual intercourse. The data about the history of diagnosis, treatment and the results of laboratory analysis of the women were extracted from the women's medical charts in the clinics. Clinical signs, urine analysis and urine cultures were used for the diagnosis of UTI in the case group by an expert obstetrician working in the prenatal care clinic. Based on the clinical signs of UTI, urinalysis and urine cultures results of patients were divided into acute pyelonephritis (APN) and acute cystitis groups. The clinical signs of UTI were defined by dysuria, urgency, and frequency of urination for acute cystitis, or the presence of fever (>38 °C), chills, vomiting, nausea and/or loin pain, with and without symptoms of cystitis for acute pyelonephritis. Abnormal urine analysis were pyuria (more than 10 leukocytes per microscopic field) and red blood cells and positive nitrite test [4,30]. Blood cultures were collected in patients with acute pyelonephritis only in cases of diagnostic uncertainty [31]. Gestational age was estimated based on the last menstrual period. BMI was calculated using height and weight measurements and classified into the following categories: normal 18.5 $\leq$ BMI $\leq$ 24.9 kg/m^2; underweight BMI < 18.5 kg/m^2; overweight 25.0 $\leq$ BMI $\leq$29.9 kg/m^2; and obese BMI $\geq$ 30.0 kg/m^2.Then, 2 ml of blood sample was taken from peripheral vein to measure serum vitamin D levels.

Diagnostic assessment

Urinary tract infection was diagnosed with a midstream urine samples in HiCrome UTI Agar (Himedia) plate. The plates were incubated under aerobic conditions at 37 °C and read after 48 h. The growth of more than 10^5 colony-forming units of one organism per milliliter on the urine culture plate was considered positive [4,30]. For measurement of serum vitamin D levels, after blood sampling and centrifugation, serums were isolated from samples and were kept at 2–8 °C until test performance. The assay was performed within 120 h of sample collection. Serum vitamin D levels were measured for 187 pregnant women based on the CLIA[2] method using Liaison 25 OH Vitamin D Total Assay (DiaSorin; USA).We classified vitamin D deficiency as serum vitamin D levels of less than 20 ng/mL, insufficiency as 21–29 ng/mL, and sufficiency as 30–100 ng/mL according to recent Clinical Guidelines Committee [32].

Sample size calculations

The sample calculation was based on the formula used for case-control study based on the data from the " Jorde R et al. (2016)" [33]

[1] -Ultraviolet B

[2] - Chemiluminescent immunoassay

The sample size was determined on the assumption of 95% confidence level ($Z\alpha/2 = 1.96$), 90% power ($Z\beta = 1.28$), with one to one ratio among cases and controls, considering 15% non-response rate the final sample size was 180 (90 cases and 90 controls).

Ethical statement

The study design was approved by the Ethics Committee (code 901.1396.PHNM.SBMU.IR) at Shahid Beheshti University of Medical Sciences in Tehran, Iran. All participants were informed about the purpose of the study and signed informed consent forms.

Data handling and Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normal distribution of data. Categorical variables were evaluated using the chi-square test or Fisher's test, as appropriate. The continuous variables were evaluated with *t*-test or Mann–Whitney U test, as, to determine differences of the variables between the two groups. A p-value of less than 0.05 was considered significant. Binary multivariate unconditional logistic regression analysis was used for adjusted confounding factors: "maternal age, level of education, monthly income, BMI" [4] with vitamin D, to determine the association between the risk factors and UTI, which was estimated by the odds ratio (OR) with a 95% confidence interval (95% CI). The data was analyzed using IBM SPSS software (version 24).

Results

This study was conducted on 187 pregnant women referred to prenatal care clinics, including 97 pregnant women with UTI (case group) and 90 pregnant women without UTI (control group). Table 1 presents the demographic and obstetrical characteristics and vitamin D levels of the participants. The average gestational age of case and control groups were 26.7. ± 11.7 vs 25.1±10.5 weeks, respectively. There was no significant difference between the two groups for, parity, trimesters of pregnancy and frequency of sexual intercourse ($p > 0.05$) but, there was a significant differences in monthly income between the two groups ($p < 0.05$). The mean of serum vitamin D levels were significantly lower in the case group versus the control group (12.7 ± 5.9 ng/ml vs 26.05 ± 10.37; $p < 0.001$).

The majority of women had serum vitamin D levels deficiency (69.5%). According to Table 2. The incidence of insufficiency or deficiency for vitamin D was 65.5% in the control group but it increased to 95% in UTI group. Significant differences were noted in the incidence of insufficiency or deficiency of vitamins D, between the two groups ($p < 0.05$; Table 2).

Table 3; presents the serum vitamin D status in the trimesters of pregnancy. The incidence of vitamin D deficiency or insufficiency was 68.4% in the first trimester, but it increased to 84.1% in the third trimester. The significant differences were noted in the incidence of insufficiency or deficiency of vitamins D, between the trimesters of pregnancy ($p < 0.05$; Table 3).

In the present study, (72) 74.2% of pregnant women in the case group was diagnosed with cystitis and [25] 25.8% with acute pyelonephritis. There was a significant difference in serum vitamin D levels in those with acute pyelonephritis and cystitis (11.06 ± 7.53 and 13.94 ± 5.44 ng/ml; $p = 0.020$).

Table 4 exhibits the results of the multivariate unconditional logistic regression analysis. The association was evaluated between adjusted risk factors (Women age, BMI, Education, Monthly income, Serum vitamin D levels) and UTI. Vitamin D of less than 20 ng/ml (AdjOR = 3.67; 95% CI: 1.19–6.24; $p < 0.001$), was significantly associated with the risk of UTI in pregnant women after adjusting for this confounders in the multivariate unconditional binary logistic regression model.

Discussion

The results of our study support the hypothesis that serum vitamin D levels of less than 20 ng/ml in pregnant women can

Table 1
Comparison of demographic and obstetric characteristics and vitamin D levels of pregnant women between cases with UTI and controls.

Variable		Case (n = 97) n(%)	Control (n = 90) n(%)	p-value
Maternal age (Year.Mean ± SD)		26.4 ± 4.49	27.5 ± 4.69	0.106^
Monthly income	Low	(72) 74.%	(53) 60%	**0.034**#
	Moderate	(20) 20.7%	(28) 29.7%	
	High	(5) 5.3%	(9) 10.3%	
Education	University	(16)16.5%	(21) 22.2%	0.355#
	High school	(31) 32.4%	(33) 39%	
	Middle School	(22) 22.6%	(16) 17.3%	
	Primary School	(23)23.4%	(17) 18%	
	Illiterate	(5) 5.1%	(3) 3.5%	
parity	One	(28) 29.3%	(23) 25.6%	0.597#
	Two	(38) 38.9%	(40) 44.2%	
	Three	(24) 24.4%	(21) 22.7%	
	Four	(7) 7.3%	(6) 7.8%	
BMI	Normal (18.5-24.9 kg/m^2)	(54) 56.7%	(50) 57.8%	0.625*
	Over weight (25-29.9 kg/m^2)	(43) 43.3%	(40) 42.2%	
Gestational age	First trimester	(22) 22.6%	(24) 26.7%	0.570#
	Second trimester	(26) 26.6%	(26) 28.9%	
	Third trimester	(49) 50.8%	(40) 44.4%	
Sexual intercourse per week	No time	(12) 11.3%	(11) 14.4%	0.354#
	Once	(23) 24.1%	(22) 23.3%	
	Twice	(34)35 %	(35) 37%	
	Three times	(20) 20.8%	(16) 17.8%	
	Four times	(8) 8.8 %	(6) 7.5%	
Serum vitamin D levels (ng/ml.Mean ± SD)	Serum vitamin D<20	10.5 ± 3.52	13.80 ± 3.90	<**0.001**#
	21≤ Serum vitamin D ≤29	23.37 ± 1.91	25.29 ± 1.90	
	Serum vitamin D ≥30	32.30 ± 3.80	45.75 ± 10.64	

^ Student *t*-test.
# Mann-Whitney values are presented as mean ± standard deviation.
* Chi-square values are presented as number (%).

Table 2
The serum vitamin D levels in pregnant women.

Variable	Pregnant women (n = 187)n(%)	Case (n = 97) n(%)	Control (n = 90) n(%)	p-value
Vitamin D deficiency	130(69.5%)	83(85.7%)	47(52.2%)	<0.00*
Vitamin D insufficiency	21(11.2%)	9(9.3%)	12(13.3%)	
Vitamin D sufficient	36(19.3%)	5(5.2%)	31(34.4%)	

* Chi-square values are presented as number (%).

Table 3
The serum vitamin D levels in the trimesters of pregnancy.

Variable	First trimester (n = 46)n(%)	Second trimester (n = 52) n(%)	Third trimester (n = 89) n(%)	p-value
Vitamin D deficiency	29(64.1%)	37(69.7%)	64(72.5%)	0.018*
Vitamin D insufficiency	2(4.3%)	9(20.2%)	10(11.6%)	
Vitamin D sufficient	15(31.6%)	6(10.1%)	15(15.9%)	

* Chi-square values are presented as number (%).

Table 4
Multiple binary logistic regression analysis of adjusted risk factors for UTI.

		Multiple logistic regression	
Variable	Category	Adjusted OR (95% CI)	p-value
Women age	18-23 year	1(Reference)	
	24-29 year	0.57(0.22-1.48)	0.25
	30-35 year	1.13(0.53-2.41)	0.73
BMI	Normal	1(Reference)	
	Over weight	1.10 (0.54-1.85)	0.78
Education	University	1(Reference)	
	High school	0.74 (0.18-3.46)	0.28
	Middle school	0.58 (0.20-1.63)	0.30
	Primary school	1.28 (0.88-2.15)	0.63
	Illiterate	1.26 (0.98-2.80)	0.74
Monthly income	High	1(Reference)	
	Moderate	0.97 (0.43-2.16)	0.941
	Low	1.64(0.88-3.07)	0.119
Serum vitamin D (n g/ml)	Serum vitamin D ≥30	1(Reference)	
	Serum vitamin D<20	3.67 (1.19-6.24)	<**0.001**
	21≤ Serum vitamin D ≤29	0.44(0.17-1.15)	0.097

increase the risk of UTI in pregnancy. Women who had serum vitamin D levels of less than 20 ng/ml were more likely to have UTI in pregnancy than women with Serum vitamin D of more than or equal to 30 ng/ml after adjusting for confounders. This association was also observed in the other case-control studies on children, infant and premenopausal women. A study in Iran, on 70 children under three years of age with UTI showed that serum vitamin D levels in patients with UTI are significantly lower than the control group, and vitamin D deficiency is a risk factor for UTI, especially in girls [25]. Nseir et.al (2013) in Israel, indicated that vitamin D deficiency is a risk factor for recurrent UTIs in premenopausal women [26]. Nielsen.et.al (2014) conducted a study on forty-seven UTI patients and 50 controls of healthy premenopausal, adult women. They reported, that the case group had significantly lower serum vitamin D levels, and Cathelicidin (LL-37) in urine than those of controls. The authors concluded that low levels of LL-37 can increase the probability of UTI [14]. Tekin et al. (2015) found that the serum vitamin D levels among children with UTI were significantly lower than healthy controls [34]. In addition, Yang et -al. (2016) study on 132 infants experiencing a first episode of UTI and 106 controls, aged 1–12 months showed that the mean serum vitamin D levels in the case group with UTI were significantly lower than the control group [35].

Our study also showed a significant difference in serum vitamin D levels between the women with pyelonephritis and cystitis. β-defensins have been proven to increase during pyelonephritis and its expression increases in renal tubules epithelium; It is known as a potential mechanism of antimicrobial defense [36,37]. Moreover, human resistance to producing antimicrobial peptides such as, cathelicidin and β-defensins is correlated with bacterial invasive infection to the upper urinary tract [37,38]. Vitamin D is known as a potent inducer of antimicrobial peptides such as human cathelicidin and β-defensins [17,39]. Previous in vitro studies demonstrated that intracellular bacterial colonies in the urinary bladder of vitamin D-deficient human and mice spread to the upper urinary tract and led to a disordered cytokine response to infection. [15,17]. In accordance with these results, Yang.et.al (2016) conducted a case control study on 238 infants revealing that infants with acute pyelonephritis had lower serum vitamin D levels than those with cystitis [35]. Shalaby. et.al (2016) carried out a prospective case-control study including 50 children with first febrile UTI and 50 with no risk factors for UTI (control). They found that patients with lower UTI had significantly higher serum vitamin D levels compared to those with acute pyelonephritis [40]. Tekin et al (2015) conducted a prospective study on 82 children experiencing a first episode of UTI and 64 healthy control children. They also showed that serum vitamin D levels were significantly lower in patients with acute pyelonephritis compared to patients with lower UTI [34]. On the contrary, a case control study on 70 children under 12 years of age with UTI showed that there was no significant difference between acute pyelonephritis and cystitis in terms of serum vitamin D level. This may be due to their small sample size. [24].

A high prevalence of vitamin D deficiency in pregnant women has been reported from different regions around the world [41–45]. In our study vitamin D deficiency (less than 20 ng/mL) was diagnosed in 69.5% of pregnant women, and prevalence of vitamin D deficiency or insufficiency in late pregnancy was higher than early pregnancy. Several studies also observed a significant decrease in serum vitamin D levels towards the end of pregnancy [46–50]. These studies reported that the increased demands of calcitriol in the third trimester of pregnancy can lead to a reduction in the serum concentrations of vitamin D in the third trimester of pregnancy. These results may be related to the fact that in the third trimester of pregnancy, near to 25–30 g of calcium are transferred to the growing fetus, a period in which, if compared to the other trimesters, there is greater maternal demand for vitamin D.

Urinary tract infections (UTI) are common in women who are pregnant and may cause serious adverse pregnancy outcomes for both mother and child. Increasing women's awareness of the importance of vitamin D for good health and sources of vitamin D (from safe sun exposure as the main source, and limited dietary intake including; oily fish egg yolk, red meat) can improve the vitamin D status and outcomes in pregnancy. Since vitamin D can be synthesised in the skin upon exposure to sunlight, increasing casual sun exposure for reaching the optimal serum levels has been recommended [8]. However, there are many causes that interfere with vitamin D synthesis in the skin, including heritable disorders of vitamin D synthesis in the skin, exposure time of the day, season, latitude, dark skin and air pollution [51]. So taking vitamin D supplements may be the best way to prevent UTI in pregnant women. However, recent recommendations suggest that pregnant and breastfeeding women require at least 2000 IU/day supplement of vitamin D, to prevent vitamin D deficiency [52].

This case control study explored the relationship between serum vitamin D levels and UTI in pregnant women for the first time. Inaccurate responses about the frequency of sexual intercourse by the participants may be a limitation of this study. Prospective studies are recommended for investigating the Vitamin D levels and UTI in pregnancy.

Conclusion

This study revealed that pregnant women with low serum vitamin D levels were more at risk for UTIs during pregnancy. The prevalence of UTI during pregnancy is high and prevention of UTI is sensible during pregnancy. The use of vitamin D supplement may be useful for the prevention of UTIs. More studies in different settings and geographical regions are recommended.

Authors' contributions

SH designed the study, collected, analyzed the data, interpreted and drafted the manuscript. FP was supervisor of this study and contributed to the study design, data analysis and drafting of the manuscript. SD and TB and RH were the advisors of the study and contributed to the design. MK contributed to the data analysis. All authors reviewed the manuscript and approved the final manuscript.

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Declaration of Competing Interest

The authors of this article do not have any conflict of interest.

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