Original Article

# The Correlation Between Serum Vitamin D and Urinary Tract Infection in Pregnant Woman : A Case Control Study

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## ABSTRACT

**Background:** Urinary tract infection (UTI) during pregnancy is common due to a unique state of physiological, immunological and hormonal changes, increased vesicoureteral reflux and urinary tract obstruction by the uterus. Vitamin D is important for human health, being more crucial during pregnancy. A third of the population are estimated to suffer from Vitamin D deficiency. Studies recently have been focused on the effect of vitamin D deficiency on the immune system, both the innate and adaptive. Vitamin D has been found to enhance the innate immune system

**Aim:** We aim in this study to investigate the link between serum vitamin D levels and UTI in pregnant women.

**Materials and Methods:** A case control study conducted between September 2020 and June 2021 at the prenatal care clinic of the Kasr Al-Ainy University Hospital. The study population consisted of 200 eligible pregnant women, screened and recruited from pregnant women seeking management for symptomatic UTI or for routine prenatal care.

**Results:** In total of 200 pregnant women referred to prenatal care clinics, 100 pregnant women with UTI (case group) and 100 pregnant women without UTI (control group). Serum vitamin D levels were significantly lower in the cases compared to the control group (14.51 ± 5.32 versus 18.7 ± 7.05; $p<0.001$). The multivariate logistic regression analysis shows the association between adjusted risk factors (age, BMI, education, frequency of intercourse and serum vitamin D levels) and UTI. Deficient serum vitamin D levels was significantly associated with a risk of UTI in pregnant women (OR = 0.221; 95% CI: 0.100-0.487) after adjusting for these confounders

**Conclusion:** Vitamin D deficiency has a significant and direct relationship with the prevalence of UTI in pregnant women. RCTs are needed to assess the optimum vitamin D threshold, and to assess levels that could prevent the complication of UTI in pregnant women.

**Key Words:** Pregnant woman, serum vit D, urinary tract infection

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## INTRODUCTION

Urinary tract infection (UTI) during pregnancy is common due to a unique state of physiological, immunological and hormonal changes, increased vesicoureteral reflux and urinary tract obstruction by the uterus[1]. Activation of the innate system and suppression of the adaptive system are major changes of the immune system resulting in more susceptibility to infections during pregnancy[2-4]. Estimated incidence of acute cystitis is 1% - 2% of pregnant women and of acute pyelonephritis is 0.5% - 2%[5], although the overall incidence has been reported to reach 8% in some studies[2,6]. UTIs in pregnancy can result in serious adverse maternal and fetal outcomes. Recent studies have reported links with chorioamnionitis, intrauterine growth restriction (IUGR), low birth weight, preterm delivery and maternal systemic infections[2,7,8,9]. Some studies have even reported an increase in perinatal mortality [4,6]. A quarter of healthy women have a six month risk of recurrence following a first UTI[10], with around five percent of women with an initial UTI developing multiple episodes within a year[10]. Although UTI infection may result in subsequent morbidity, the use of antibiotics for treatment, recommended by most guidelines[11], merits the same attention. Evidence has proven that treatment of UTI and asymptomatic bacteriuria results in the reduction of pregnancy complications such as IUGR and preterm delivery[12,13]. However, studies have also reported pregnant women taking antibiotics could also affect their growing fetus and its immune system[14]. Known risk factors for UTI in pregnancy include previous UTI, anatomic and functional urinary tract abnormalities, increased body mass index (BMI) and frequency of sexual activity, multiparity, diabetes mellitus (DM), low socioeconomic status[15,16] and asymptomatic bacteriuria (1.9 – 15% of pregnant women[17].

Vitamin D is important for human health, being more crucial during pregnancy[18]. A third of the population are estimated to suffer from Vitamin D deficiency, with more

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than 80% thought to be prone in people in Africa and Asia[19-22]. Reduction in the level of vitamin D may develop during pregnancy[23], with several studies observing a significant decrease by the end of pregnancy[24-28] as a result of increased demands of calcitrol, possibly due to the transfer of near to 25-30g of calcium to the growing fetus. Vitamin D deficiency has been long been associated with many adverse health consequences, notably osteoporosis and autoimmune diseases such as preeclampsia[29-31]. Studies recently have been focused on the effect of vitamin D deficiency on the immune system, both the innate and adaptive[32]. Vitamin D has shown to enhance the innate immune system by inducing antimicrobial peptides such as cathelicidin and β- defensins, that assists in infection prevention. Additionally, vitamin D modulates the adaptive immune system by the secretion of cytokines from lymphocytes and by inhibiting inflammation[33]. The urinary tract is commonly attacked by many pathogens and rapid, effective defence mechanisms are needed to prevent the development of UTIs. In*vitro* evidence have found that deficiency of vitamin D results in the failure of the bladder epithelial cells to secrete cathelicidin which would otherwise protect the lower urinary tract[34,35].

The emphasis of previous reviews and metanalysis, have been from research that indicate a link between vitamin D status and pregnancy complications such as gestational diabetes mellitus (GDM), preeclampsia, and risk of cesarean section, as well as to length of gestation and fetal growth[36-40]. Recent research has found associations between vitamin D deficiency and an increase in the frequency and severity of bacterial infections of the respiratory and urinary tract[34,35], although numerous controversies have been reported[41-43]. There is limited evidence to conclude a link between vitamin D levels and UTI during pregnancy with one recent study, to our knowledge, focusing on the association between serum vitamin D levels and UTI in pregnant women[44]. An essential factor of prenatal care is the prevention of UTI in pregnancy which consequently would improve maternal and neonatal health and lower the risk of preterm delivery[45]. Due to the limited evidence in the literature, we aim in this study to investigate the link between serum vitamin D levels and UTI in pregnant women.

## PATIENTS AND METHODS

A case control study conducted between September 2020 and June 2021 at the prenatal care clinic of the General Cairo University Hospital, after approval from the ethics committee. The study population consisted of 200 eligible pregnant women, screened and recruited from pregnant women seeking management for symptomatic UTI or for routine prenatal care.

The recruitment of 100 pregnant women diagnosed with symptomatic UTI (case group) were compared with an equal number of pregnant healthy women (control group) with neither symptomatic UTI nor asymptomatic bacteriuria. Efforts were made to match cases and controls by parity, trimesters of pregnancy and frequency of intercourse. Pregnant women eligible for recruitment were required to be between 18 and 40 years of age with a BMI not exceeding 35 (class II). Exclusion criteria included a history of recurrent UTI, anaemia, diabetes, asymptomatic bacteriuria, urinary tract anomalies, urinary tract stent placement, kidney stones, urinary incontinence, neurogenic bladder, or substance abuse and immune system inhibitory drug intake. Women receiving antibiotics in the last six months were also excluded from the study.

All women fulfilling the study criteria were counselled to participate in our study after which an informed written consent was obtained from all participants. Data was collected in the prenatal care clinic using a questionnaire that collected information on demographic characteristics, obstetric history and the frequency of sexual intercourse.

Diagnosis of UTI was by clinical signs, urine analysis and culture, and based on these results participants were classified as healthy or positive for UTI (acute cystits or acute pyelonephritis (APN). Clinical examination of all women was performed with acute cystitis defined by urgency, frequency of urination, dysuria, hematuria and pyuria. If fever (>38°), chills, vomiting, nausea and/or loin pain, with or without symptoms of acute cystits was detected, APN was suspected. Laboratory diagnosis of UTI involved taking a clean catch mid stream urine sample, collected in a clear, dry, sterile container with a tight fitting lid, from each patient. The samples were labelled and transported to the main laboratory for urine analysis and culturing. Abnormal urine analysis was defined by pyuria (ten leukocytes or more per microscopic field), red blood cells and positive nitrite test[15,46]. Diagnosis of UTI was confirmed by culture of the midstream samples in agar plates in aerobic conditions at 37°C, read after 48 hours. A positive culture was recorded when $10^5$ colony forming units (CFU)/mL of a single organism was found[15,46].

Venous blood samples were taken from all participants for measurement of serum Vitamin D levels by ELISA method in the hospital laboratory. Vitamin D levels were categorised into three categories according to the recent Clinical Guidelines Committee; sufficiency as 30ng/mL or more, insufficiency as 21-29 ng/mL and deficiency as 20ng/mL or less[47]. Measurement of haemoglobin concentration was also assessed to exclude anemia.

The primary study outcome was to determine the association between serum vitamin D levels and UTI in pregnant women. Secondary outcomes include identifying trends regarding the relationship between serum vitamin D levels and the severity of UTI in pregnant women, trimesters of pregnancy, parity, BMI and education level.

Calculation of sample size was based on the information from the 'Jorde R *et al*. (2016)[48]. With an assumption of 95% confidence level (Zα/2 = 1.96), 90% power (Zβ _= 1.28), and among cases and controls a ratio of one to one, taking into consideration 15% non-response rate the final sample size was 200 (100 cases and 100 controls).

## STATISTICAL ANALYSIS

Data were statistically expressed in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the standard assumption using Kolmogorov Smirnov test. Because the main groups were large enough, numerical variables were compared using Student t test for independent. For comparing categorical data, Chi-square ($\chi^2$) test was performed. When the expected frequency was less than five, the exact test was applied. Multivariate logistic regression analysis was utilized to investigate the major independent risk factors for the occurrence of UTI. A statistically significant outcome was considered when the two-sided p values were less than 0.05. Statistical analysis were made by computer program IBM SPSS .

## RESULTS

This study was conducted on 200 pregnant women referred to prenatal care clinics, 100 pregnant women with UTI (case group) and 100 pregnant women without UTI (control group). The mean of age and BMI was slightly higher in the cases compared to the controls but did not reach statistical significance. Serum vitamin D levels were significantly lower in the cases compared to the control group (14.51 ± 5.32 versus 18.7 ± 7.05; $p<0.001$) (Table 1).

Table 2 presents percentages of, and comparisons between the demographic, obstetrical characteristics and vitamin D levels of the participants within both groups. There was no significant difference between incidence in the two groups for age, BMI, parity, pregnancy trimesters, education and frequency of sexual intercourse subgroups ($p > 0.05$). The majority of women in our study were found to be deficient for serum vitamin D <20ng/mL (74%). The incidence of women with deficient serum levels of vitamin D was significantly higher in the case group compared to the control group (90% versus 58%; $p<0.001$) (Table 2).

The multivariate logistic regression analysis shows the association between adjusted risk factors (age, BMI, education, frequency of intercourse and serum vitamin D levels) and UTI. Deficient serum vitamin D levels was significantly associated with a risk of UTI in pregnant women (OR = 0.221; 95% CI : 0.100-0.487) after adjusting for these confounders (Table 3)

Table 4 exhibits the demographic and obstetric characteristics and the relationship with different serum vitamin D levels for all participants in the study. The incidence of vitamin D deficiency did not statistically differ with increase in age in the participants (p=0.172), however the incidence did significantly increase with increasing BMI, parity and trimester. The incidence of serum vitamin D deficiency also increased with reduced levels of education. A significant difference in the incidence of deficient serum vitamin D levels was also found between those with acute cystitis and acute pyelonephritis (89.7% versus 100%; *p<0.001*) (Table 4).

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

| | Group | | | *P-value* |
|---|---|---|---|---|
| Variables | Control | Cases | Total | |
| Age | 27.89±4.54 | 28.35±4.55 | 28.12±4.54 | 0.475 |
| BMI | 28.30±2.63 | 28.92±2.78 | 28.61±2.72 | 0.110 |
| Serum vitamin D | 18.70±7.05 | 14.51±5.32 | 16.61±6.58 | 0.000* |

Data are presented as mean ± standard deviation

**Table 2:** Comparison of demographic and obstetric characteristics and vitamin D levels of pregnant women between cases and controls

| | | Group | | | *p-value* |
|---|---|---|---|---|---|
| Variable | | Control (n=100) n (%) | Cases (n=100) n (%) | Total | |
| Maternal Age | 18-24y | (25) 25% | (19) 19% | (44)22% | |
| | 25-30y | (43) 43% | (48) 48% | (91)45% | 0.575 |
| | >30y | (32) 32% | (33) 33% | (65)32.5% | |
| BMI | 18-24.9kg/m2 | (11)11% | (11) 11% | (22) 11% | |
| | 25-29.9kg/m2 | (63)63% | (53) 53% | (116) 58% | 0.290 |
| | >30kg/m2 | (26)26% | (36) 36% | (62) 31% | |
| Parity | Primigravida | (34) 34% | (30) 30% | (64) 32% | |
| | 1 or 2 | (60) 60% | (56) 56% | (116) 58% | 0.166 |
| | >2 | (6) 6% | (14) 14% | (20) 10% | |
| Trimester | 1 | (19) 19% | (28) 28% | (47) 23.5% | |
| | 2 | (36) 36% | (33) 33% | (69) 34.5% | 0.319 |
| | 3 | (45) 45% | (39) 39% | (84) 42% | |
| Education | University | (12) 12% | (10) 10% | (22) 11% | |
| | High school | (39) 39% | (23) 23% | (62) 31% | |
| | Middle school | (37) 37% | (47) 47% | (84) 42% | 0.111 |
| | Primary school | (10) 10% | (17) 17% | (27) 13.5% | |
| | Illiterate | (2) 2% | (3) 3% | (5) 2.5% | |
| SI frequency | 0-1/week | (75) 75% | (65) 65% | (140) 70% | |
| | 2 or 3/week | (23) 23% | (30) 30% | (53) 26.5% | 0.232 |
| | >3/week | (2) 2% | (5) 5% | (7) 3.5% | |
| Serum vitamin D | <20ng/mL | (58) 58% | (90) 90% | (148) 74% | |
| | 21-29ng/mL | (35) 35% | (8) 8% | (43) 21.5% | 0.000* |
| | >30ng/mL | (7) 7% | (2) 2% | (9) 4.5% | |

Data are presented as frequencies and n (%).

**Table 3:** Multiple logistic regression analysis of adjusted risk factors for UTI

| Variable | OR (95%CI) | *P-value* |
|---|---|---|
| Age | 1.094 (0.731-1.636) | 0.663 |
| BMI | 0.863 (0.549-1.357) | 0.523 |
| Education | 0.960 (0.611-1.507) | 0.858 |
| Frequency of intercourse | 1.853 (0.578-5.936) | 0.299 |
| Serum Vitamin D | 0.221 (0.100-0.487) | 0.000* |

**Table 4:** Risk factors and serum vitamin D levels

| Variables | | Serum vitamin D | | | *p-value* |
|---|---|---|---|---|---|
| | | Deficiency <20ng/mL | Insufficiency 21-29ng/mL | Sufficiency >30ng/mL | |
| Age | 18-24y | (30) 68.2% | (12) 27.3% | (2) 4.5% | |
| | 25-30y | (67) 73.6% | (17)18.7% | (7) 7.7% | 0.172 |
| | >30y | (51) 78.5% | (14)21.5% | (0) 0% | |
| BMI | <25kg/m2 | (10) 45.5% | (8) 36.4% | (4) 18.2% | |
| | 25-30kg/m2 | (82) 70.7% | (29) 25% | (5) 4.3% | 0.000* |
| | >30kg/m2 | (56) 90.3% | (6) 9.7% | (0) 0% | |
| Parity | Primigravida | (36) 56.3% | (21) 32.8% | (7) 10.9% | |
| | 1 or 2 | (92) 79.3% | (22) 19.0% | (2) 1.7% | 0.000* |
| | >2 | (20) 100% | (0) 0% | (0) 0% | |
| Trimester | 1 | (30) 63.8% | (11) 23.4% | (6) 12.8% | |
| | 2 | (47) 68.1% | (20) 29% | (2) 2.9% | 0.003* |
| | 3 | (71) 84.5% | (12) 14.3% | (1) 1.2% | |
| Education | High school/University | (35) 41.7% | (40) 47.6% | (9) 10.7% | |
| | Middle school | (81) 96.4% | (3) 3.6% | (0) 0% | 0.000* |
| | Illiterate/ Primary school | (32) 100% | (0) 0% | (0) 0% | |
| Severity of UTI | Absent | (58)58% | (35) 35% | (7) 7% | |
| | Cystitis | (87) 89.7% | (8)8.2% | (2) 2.1% | 0.000* |
| | Pyelonephritis | (3) 100% | (0) 0% | (0) 0% | |

Data are presented as frequencies and n (%)

## DISCUSSION

This case control study supports the hypothesis that deficient levels of serum vitamin D (< 20ng/mL) is associated with an increased risk of UTI in pregnant women. After adjusting for confounders, pregnant women were more likely to be diagnosed with an UTI if their serum vitamin D level was found to be deficient (OD 0.221; 95% CI: 0.100-0.487; $p$<0.0001) than if their levels were insufficient or sufficient. This finding agrees with most other studies that explored the correlation of the level of serum vitamin D levels with the risk of UTI, though only one to our knowledge has focused the attention of their study on pregnant women.

S. Haghdoost *et al*. (2019) conducted a study on 187 pregnant women with more than half diagnosed with 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 confounders were adjusted [44]. S.B. Ali *et al*. (2020) carried out a case control study on 75 women of reproductive age with UTI and 35 controls, and found a major link between vitamin D deficiency and UTIs mainly in moderate and severe infections , this indicated that vitamin D is a risk factor for urinary tract infection[49]. Nielsen.et.al (2014) performed a study on premenopausal women, 47 patients with UTI and 50 controls, and showed that the case group had markedly lower serum vitamin D and cathelicidin (LL-37) values in urine than control group . Low levels of LL-37, was concluded by the authors, to increase the probability of UTI[50]. Nseir et.al (2013), followed up 265 premenopausal women, 93 of which met the inclusion criteria for recurrent UTIs and recorded significantly reduced serum vitamin D levels in cases when compared to controls (9.8ng/mL ± 4 vs. 23ng/mL ± 6 respectively; $p$<0.0001). Multivariate analysis showed that a serum vitamin D <15 ng/ml (OR 4.00, 95% CI 3.40–4.62; $p$ = 0.001), was associated with recurrent UTIs in premenopausal women[51].

With regards to studies exploring the association of serum vitamin D and UTI in children, most were also in agreement with our study. A recent metanalysis by Deng *et al*. (2019) reported a correlation between a deficiency in vitamin D in children with UTI reporting an odds ratio of 3.01[52]. Georgieva V *et al* (2019), Yang *et al*. (2016), Shalaby et.al (2016), Tekin *et al*. (2015) and Katikaneni R *et al*. (2009), all also found that values of vitamin D in children who have UTI were markedly less than the non UTI children and was an self-determining cause for UTI[53-57].

In contrast to most studies, Noorbaksh *et al* (2019) and Sherkatolabbasieh *et al*. (2020) did not find any significant difference in serum vitamin D levels in children with UTI to those without, with the former study reporting lower zinc levels to be the independent risk factor[58,59]. This could be explained by small sample sizes in both studies. Moreover, Mahyar *et al*. (2018) compared 70 children with UTI to 70 matched controls and reported significantly higher levels of vitamin D in those with UTI (20.4 in the case group and 16.9 ng in the control group, $P$ = 0.01). The authors concluded that excess serum vitamin D levels in children, the result of supplementation, seemed to play a role in the pathogenesis of UTI. This was attributed to several mechanisms such as the creation of a slight nephrocalcinosis, known to be an excellent context for bacterial growth and an unregulated hyperactive immune response to an overload of serum vitamin D. Sample size was also a limitation with further studies recommended[60].

In this study, serum vitamin D deficiency was more prevalent in pregnant women with acute pyelonephritis compared to those with acute cystits. Haghdoost *et al*. (2019), Yang.*et al*. (2016), Shalaby. *et al.* (2016) and Tekin *et al.* (2015) all reported similar finding in their studies[44,54-56]. This finding supports an inverse relationship between the serum level of vitamin D and the severity of the UTI. This could be explained by proven evidence, reporting an increase of β- defensins and its expression within epithelium of the renal tubules during pyelonephritis, which is the body's mechanism of antimicrobial defence[61,62]. Vitamin D is known as a potent inducer of β- defensins and other peptides such as cathelicidin[63,64]. In *vitro* studies demonstrated that resistance to the production of this peptide, seen in vitamin D deficient humans and mice, is correlated with bacterial invasive infection of the upper urinary tract[64, 65].

A high prevalence of vitamin D deficiency has been reported in pregnant women from different areas around the world[66-69]. Our study found 74% of our sample of pregnant women diagnosed with vitamin D deficiency (less than 20 ng/mL). Women in the Middle East and Africa have been found to have a higher rate of vitamin D deficiency, which may be explained by hot weather and the practice of wearing a veil, which would result in less exposure to sunlight, a main source of vitamin D[70,71].

A significant increase in the prevalence of deficient serum vitamin D levels could be seen later in pregnancy when compared to early pregnancy, which is in agreement with other studies[24-28] that have explained this finding due to increase demands of calcitrol towards the end of

pregnancy. Moreover, this study found that the prevalence of deficient serum vitamin D levels was significantly higher with an increase in BMI, parity and with lower levels of education. Obesity is recognized to be linked with vitamin D deficiency due to its sequestration in adipose tissue, making an inverse association between BMI and vitamin D[33,72-75].

Thus, our results are compatible with a recent study that revealed that vitamin D deficiency is more predominant in obese ladies. Additionally, although sun exposure and dietary intake of vitamin D rich food can improve vitamin D status, other factors may interfere with production of vitamin D in skin such as heritable disorders, dark skin and air pollution[76]. Recommendations have suggested that pregnant women may need a minimum of 2000IU/day supplement of vitamin D to prevent vitamin D deficiency[47]. Those of lower educational background are found to less likely sustain a regular intake of pregnancy supplements, which could explain a greater incidence of vitamin D shortage with lower levels of education.

The authors of the recent update of the Cochrane Collaboration systematic review and metanalysis on the recommendation of vitamin D supplementation during pregnancy have not included any evidence on the link of vitamin D deficiency with the risk of UTI in pregnant women, but rather have recognised its link with other complications of pregnancy, namely preeclampsia, postpartum bleeding, gestational diabetes, low birth weight and preterm delivery[77,78]. The strength of this study is that only one other study, to our knowledge, has focused the attention to explore the association of serum vitamin D levels with the serious risk of UTI during pregnancy.

As of the end of 2019, the World Health Organization (WHO) has not recommended vitamin D supplementation for pregnant women to improve maternal and perinatal outcomes[79].

Prenatal vitamin D supplementation has been proven to rise fetal and maternal vitamin D levels , with no proven perinatal outcome[78].

There is no standardized for vitamin D levels for non pregnant or pregnant females with possible complications for excess vitamin D as nephritic syndrome[80].

So in order to help establish guidelines to decrease complications of UTI during gestation we need to answer 2 questions ; what is the optimum vitamin D that decrease perinatal problems and what is the adequate amount of vitamin D to reach the optimum vitamin D value.

## CONCLUSION

To conclude, this study has showed that vitamin D deficiency has a significant and direct relationship with the prevalence of UTI in pregnant women. The prevention of UTI during pregnancy can improve maternal and infant health and reduce the risk of preterm birth. RCTs are needed to assess the optimum vitamin D threshold, and to assess if the correction of serum levels of vitamin D to these levels could prevent the complication of UTI in pregnant women.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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