ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Effect of Monthly Vitamin D Supplementation During Pregnancy Versus Counseling for Increased Dietary Intake on Vitamin Serological Level and Development of Adverse Effects.

Zahraa Abdul Jaleel Murtadha*, Mahmood A Abdulrahman, and Hussam Dawood Saeed.

College Of Medicine, AL-Iraqia University, Baghdad, Iraq.

ABSTRACT

Vitamin D deficiency (VDD) is a common health problem worldwide , vitamin D status during pregnancy is of tremendous importance to the growing fetus, as the fetus here completely relies on this source during this period of its development. Vitamin D supplements during pregnancy improve the woman's vitamin D serum levels, with many other health benefits, like reducing the risk of preterm labor (less than 37 week gestation), the risk of a low birth weight baby (less than 2500 g), and the risk of developing a high blood pressure. For this reason, many health organizations have recommended vitamin D supplementation during pregnancy; still no evaluation has been made regarding the maternal adverse effects possibly encountered upon such supplement prescription, nor for the relationship between such supplementation (during pregnancy) with urolithiasis. Objectives of our cohort study on 50 pregnants are to compare between vitamin D supplementation in a monthly injection form (which as we think is more applicable than the daily basis regimen) versus adopting the strategy of non-supplementation and offering pregnant the advice to increase the vitamin resource consumption on the ultimate vitamin levels in serum, as well as on the development of adverse health outcomes (adverse symptoms and urolithiasis). The significance of our study, therefore, comes for too many reasons: the current estimates of a global pandemic of vitamin D deficiency affecting some one billion of all age and ethnic groups in including pregnant , yet with the absence of clear data about vitamin level among the pregnants in our population to justify for routine vitamin D prescription without at least evaluating its possible adverse effects including urolithiasis, finally and above all, the absence of a previous similar study in the region, since most guidelines abroad recommending this supplementation depended on the presumption of vitamin D deficiency and have been set to their pregnant population in their living setting, and their population characters. Results revealed that both groups had increment in mean of their serum vitamin D3 level, being higher in the supplemented one (41.4 versus 37.8 mean levels); though changes in both groups were not statistically significant possibly due to small sample size (in supplemented group T=0.2910, P value=0.39919; in non-supplemented T=0.0904, P value= 0.4468). No statically significant difference in the incidence of adverse symptoms was found (X2 = 0.0849, P=0.77099), and the relative risk of vitamin supplementation in predisposing to adverse symptoms was 0.9 (non-risky). There was a higher incidence of urolithiasis in the supplemented group (three versus one case), still with no statistically significant difference for same above reason (X2=1.087, P=0.2971), yet the relative risk of vitamin supplementation in predisposing to it was calculated to be 3 (risky). In view of those results, we recommend monthly vitamin D supplementation being associated with higher serum level improvement without higher incidence of adverse symptoms, though the higher incidence of urolithiasis would worth further studies on a larger study sample to search for the statistical significance.

Keywords: Vitamin D, VDD, Pregnancy.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Vitamin D deficiency (VDD) is a common, health problem worldwide. A recent review found a high prevalence of low vitamin D status in all age groups worldwide, even in countries with sun exposure all year around. The highest reported prevalence was found in the Middle East, particularly in girls and old age groups. In pregnancy, vitamin D deficiency and insufficiency are also common, as reported in a review of 17 studies in pregnants and lactating women (1). In America for example: low vitamin D status (defined as concentrations less than 50 nmol/ L) was found in 33% of US and 24% Canadian pregnants respectively. In Europe, the prevalence was ranging between 20% in Spain to 77% in Germany (2-4). Vitamin D status during pregnancy is of tremendous importance to the growing fetus, as the fetus here completely relies on this source during this period of its development. During pregnancy, vitamin D 3 naturally increases since early times and continues to increase till delivery (5). This large increase in vitamin D 3 level appears to be dependent on available vitamin D2 levels, but independent on calcium metabolism, which is a unique feature of pregnancy that allows such high levels of vitamin D3(6). Therefore, maintaining high enough levels of vitamin D2 is essential during pregnancy but may be non feasible, on the other hand vitamin D3 supplements during pregnancy improve the woman's serum levels, may reduce the risk of delivering a baby prematurely (less than 37 week gestation), reduce the risk of a low birth weight baby (less than 2500 g), and reduce the risk of developing a high blood pressure (7). Many health organizations have recommended vitamin D supplementation during pregnancy: Nice, for example, stated in its guidelines that: all the women should be informed at booking appointment about the importance of their own and their baby's health of maintaining adequate vitamin D stores during pregnancy and while breast feeding, and in order to achieve this, women should be advised to take a vitamin D supplement of 10 mg per day, notifying that women at greater risk should even be more committed to this (8). The same recommendation was made by Myoclinic (9). In this respect, the WHO has conducted a review of all the trials of vitamin D supplementation during pregnancy, and stated in its conclusions that: it does improve the maternal serum vitamin D level at term, yet there is insufficient high quality evidence relating to the clinical effects during pregnancy, and that further rigorous randomized trials are required (10).

Similarly, Cochrane conducted a systematic review of the previous trials and published it in 2016; where a set of conclusions has been made concerning some proposed benefits of supplementation (7), still no evaluation has been made regarding the maternal, at least short term, adverse effects possibly encountered upon such supplement prescription. Among the possible adverse effects, the one which has been broadly highlighted outside pregnancy is the possibility of vitamin D contribution to urolithiasis, with conflicting results being published: some supporting (12); and others denying this relationship (13), though with questions regarding the validity, since the research did not consider sun exposure or 25(OH) D levels in its workout. Urolithiasis is highly significant during pregnancy since it is the most common cause of non obstetrical abdominal pain that requires hospitalization among pregnants (14,15). besides, it is postulated that in pregnancy, a balance exists between the stone enhancing and inhibiting factors (16); consequently, the fear that vitamin D introduction with its presumed stone enhancing effect, might disturb such balance. Surprisingly, no previous studies have been made looking for the relationship between vitamin D supplementation (during pregnancy) and urolithiasis. Objectives of our study are to compare between vitamin D supplementation in a monthly injection form (which as we think is a more feasible form than on daily basis) and adopting the strategy of mere pregnant advice to increase the vitamin source consumption on the ultimate vitamin levels in serum, as well as on the development of adverse health outcomes. The importance of our study therefore comes for the following reasons:

- Vit D deficiency or insufficiency is currently a global pandemic affecting some one billion of all age and ethnic groups, and gestational vitamin D deficiency is common(10).
- The absence of clear data about vitamin D storage among the pregnants in our population to justify for routine vitamin D prescription without at least evaluating its possible adverse effects.
- The absence of a previous (regional) trial evaluating the impact of monthly vitamin D supplementation during pregnancy on the final maternal store in our pregnant population, compared to the dietary advice alone, since most guidelines abroad recommending this supplementation depended on the presumption of vitamin D deficiency and have been set to their pregnant population in their living setting, and their population characters (7).
- The absence of previous studies pointing out clearly to the adverse effects of vitamin D supplementation during pregnancy, particularly for urolithiasis.

ISSN: 0975-8585

PATIENT AND METHODS

Time frame

Time taken for study completion, starting from the time of patient enrollment and data collection till analysis and interpretation was about two years.

Study design

The study is a prospective cohort one conducted in Spring /Summer months (March to August, 2015) on patients coming exclusively from Baghdad i.e., the same living setting. In this study fifty pregnant women presenting for routine antenatal care, who fulfilled the inclusion criteria were included. Those were then randomized into two study groups: The first one given single monthly Injections of vitamin D (120.000 I Us) at 5th, 6th, and 8th months of their gestational period, in accordance with the Myoclinic website dose recommendations for pregnants) (9). The 2nd group, just counseled and given e brochure about the importance and sources of vitamin D intake. Pregnants in both groups were then, tested for urolithiasis by urinary ultrasound and general urine exam, as well as for serological vitamin D level at 36th week of gestation and results were analyzed and compared.

Study subjects (study population)

Inclusion criteria: eligible patients were: pregnants in the first trimester (< 14 weeks gestational age, multipara ≥ 3), middle aged (20-40) of moderate skin color (neither fair, nor dark), intermediate socioeconomic class. Pregnants with those criteria, were submitted to general urine exam, urinary ultrasound and tested for serum level of vitamin D3, and only those who turned, out to be free of urolithiasis, with a normal vitamin level (20-50 ng/ml) were included in the study.

Exclusion criteria

Ebnormal vitamin D3 level in serum, current or past history of UTIs, hypertension or risk factors for it, diabetes or risk factors for it were all criteria against inclusion in the study (because of the reported effect of vitamin supplementation in predisposing to these conditions, and the subsequent risk to the patients).

Methods

Randomization:- After case eligibility determined, and informed consent taken, cases were randomized into two study arms using a computer generated randomization table.

Methods of data collection:- Data about the short term side effects of vitamin D supplementation were obtained through asking patients in both study groups to fill a questionnaire about whether they have experienced any of a list of SE as reported in literature. Data about effects of treatment versus no treatment on serological vitamin levels and predisposition to urolithiasis were obtained through submission of patients at end of study period (in both study groups) to a blood test for vitamin level, urinary ultrasound, and general urine exam, respectively.

Outcomes and statistical analysis:- Serum level at the end of pregnancy, the presence or absence of any evidence of urolithiasis, and patients' report of any associated adverse clinical symptoms were all compared between both study groups.

Study limits

The small sample size was to cope with the limited time frame allocated for the study. Data collection through a questionnaire is definitely subjective and might be affected by patients education and motivation.

RESULTS

1. Regarding the effect of vitamin D supplementation in changing vitamin serum level at end of pregnancy compared to counselling for increased dietary intake, as shown in table (1). The mean of vitamin D serum

levels for patients in each study group has been calculated at the study beginning; as well as at 36 w gestation. At beginning of study, the mean values of vitamin D levels in serum in the 1st: group (supplemented) and the second group (not supplemented) were (35,7) , (36.2) ng/ml respectively; at the end of the study those have changed to (41.4), (37.8) ng/ml respectively, with an apparent higher increase in the supplemented group. However, the change in mean values in both groups has been estimated to be non statistically significant (in supplemented group T=0.2910, P value=0.39919; in non-supplemented T=0.0904, P value= 0.4468).

2. Regarding the effect of vitamin D supplementation in predisposing to adverse symptoms compared to counselling for increased dietary intake, as shown in table (2). Among the 25 pregnants supplemented, nine patients (36%) reported adverse symptoms, among which the most commonly reported was cramps and altered bowl motion (16%), followed by headache (12%), muscle pain in (4%). Sleepiness, and hypersensitivity reaction were not encountered, in the study group. Among patients of the other group (on counselling), ten patients reported adverse symptoms and those were: cramps and altered bowl motion (12%), nausea (12%), sleepiness (1.2%), headache (4%). There was no statistically **significant** difference in the incidence of adverse clinical complaints between study groups (X2: 0,0849, P value: 0.7709). Relative risk of vitamin supplementation in predisposing to SE was 0.9

3. Regarding the effect of vitamin D supplementation in predisposing to urolithiasis compared to counselling for increased dietary intake, as shown in table (3).

Among patients of the 1st group (supplemented**),** four cases had an evidence of urolithiasis: three by just general urine exam, and one case by a concomitant ultrasound picture (crystals were calcium oxalate in three and combined calcium oxalate and amorphous mate in one case); while in the other group only one case developed calciuria by general urine exam (the ultrasound had been free). (No statically significant difference X2=1.087, P=0.2971). Relative risk of vitamin supplementation in predisposing to urolithiasis was calculated to be 3 (risky)

This study was conducted in Spring /Summer months (March to August) on patients coming exclusively from Baghdad i.e. the same living selling, for the following considerations: seasonal variation was reported to increase the risk of vitamin D deficiency in pregnancy, with a greater prevalence of this during winter months compared with summer months (17,1); this also applies for latitude where the difference has also been shown to affect the concentration of vitamin D in a majority of pregnant women (2). All the patients included in the study had normal vitamin D levels in serum, the value adopted for this was ranging between 20-50 ng/ml as stated by the institute of medicine, 2010 (18), here serum calcidiol (25 OH calciferol) is usually used to assess the vitamin status, as it reflects the sum of the vitamin D produced cutanously and that obtained from foods and supplements (19). It is important to notify that this metabolite is difficult to measure, with large variations between methods and standard ranges among laboratories even when same methods are used which may be attributed to the differences in sample pretreatment or the solvent extraction system used (20).

Table 1: Distribution of the two study groups by their mean of serological vitamin D levels at beginning and end of the study.

	Mean of vit D levels		**No. of cases**	**T and P values**
Type of intervention	At beginning of pregnancy	At the end of pregnancy		
Vit D supplementation	**35.7**	**41.4**	**25**	**T=0.29109 P value=0.39919 NS**
Counselling for increased dietary intake	**36.2**	**37.8**	**25**	**T=0.0904 P value= 0.4468 NS**
Total			**50**	

ISSN: 0975-8585

Table 2: Frequency distribution of the study groups by incidence of adverse symptoms

Type of Intervention	Adverse symptoms				Total	
	With adverse symptoms		Without adverse symptoms			
	No.	%	No.	%	**No.**	**%**
Vit D supplementation	**9**	**36**	**16**	**64**	**25**	**100**
Counselling for increased dietary intake	**10**	**40**	**15**	**60**	**25**	**100**
P=0.77099 X2 = 0.0849 NS *RR = 0.9						

***RR: relative risk of vitamin supplementation in predisposing to adverse symptoms**

Table 3: Distribution of the study groups by incidence of urolithiasis

Type of intervention	Urolithiasis				Total	
	With		Without			
	No.	%	No.	%	**No.**	**%**
Vit D supplementation	**3**	**12**	**22**	**88**	**25**	**100**
Counseling for increased dietary intake	**1**	**4**	**24**	**96**	**25**	**100**
P = 0.2971 X2=1.087 NS						

DISCUSSION

1. Concerning results of vitamin supplementation effect on changing vitamin serum level at end of pregnancy compared to non-supplementation and just dietary counselling: the increment notified in non-supplemented group consists with literature reports that vitamin D3(Calcitriol) increases since early times of pregnancy and continues to increase till delivery (5). This increase appears to be dependent on available vitamin D2 (calcidiol) levels, but independent on calcium metabolism, which is a unique feature of pregnancy which allows for high levels of vitamin D3 (6), and pointing out to the necessity of maintaining high enough levels of Calcidiol (by increased intake or supplementation) to sustain the required increased levels of Calcitriol important during pregnancy. The apparently higher change in mean values in the supplemented than in non-supplemented one (to 41.4, 37.8 ng/ml) respectively goes with previous study reports that vitamin supplementation during pregnancy improves the woman's vitamin D status at end of pregnancy (7). The finding that the change in mean values in both groups was not statistically significant (in supplemented group T=0.2910, P value=0.39919; in non-supplemented T=0.0904, P value= 0.4468) may be attributed to the small sample size. There are no available reports in literature about the value of change that vitamin D supplementation might induce or the optimal level that should be achieved upon that. There have been even a debate about the optimal method and frequency of administration; however we think that adopting the intermittent monthly dosage had the privileges of both efficacy in increasing the serum levels, as well as the possibly better compliance and less costs compared to the daily dosage.

2. Regarding results about the incidence of adverse maternal symptoms upon vitamin supplementation, the finding of no statistically significant difference in the incidence of adverse effects between the supplemented and non-supplemented groups (X2: 0,0849, P value: 0.7709) might be attributed small sample size; yet the relative risk 0.9 (non-risky) of vitamin supplementation in predisposing to side effects would support the supplementation innocence in adverse effect contribution. The finding that cramps and altered bowl motion are shared in both supplemented and non-supplemented groups would eliminate the attribution to supplementation and that they might simply be attributed to the pregnancy physiological alterations in the gastrointestinal tract. Yet the finding of headache as being responsible for 12% of reported adverse supplementation effects goes with most literature reports, and most publications about this drug do recommend avoidance of this drug among patients with headache (2). In pregnants, it is important to bear in mind that headache might not be merely a side effect of the drug, but might be a feature of preeclampsia

predisposed to by vitamin supplementation(4). some well reported adverse symptoms as sleepiness and hypersensitivity, were not encountered in the study group.

3. Concerning results of the role of vitamin supplementation in incidence of urolithiasis, to start with: the finding of 4 cases of urolithiasis among the study group of 50 pregnants is extremely high when compared with the reported incidence in literature, estimated to be in the value of 1 per 1500 (22). Again, the non-statistically significant difference from that in non-supplemented group would be attributed to the small sample size (X2:1,087, P value:0,2971). However, the relative risk of vitamin supplementation was calculated to be 3 (risky). When comparing this result with literature reports in this respect, we find that outside pregnancy, results were conflicting, some supporting: sometimes linking this effect to concomitant modern diet consumption, low latitudes, sun exposure (11), and sometimes linking the supplement independently to kidney stones (12), Other studies were denying any relationship between vitamin D use and the development of urolithiasis: the largest study searching this relationship and concluding its absence was conducted by Harvard University; upon which questions were raised for not taking in consideration the issues of sun exposure, or vitamin D storage (13). All those studies were conducted outside pregnancy, where as during pregnancy, the largest study has been conducted by Cochrane organization which reviewed all the clinical trials concerning vitamin supplementation in pregnancy, however unfortunately in that review data on adverse effects on the mother, including the possibility of kidney stone formation were not reported to compare with (7).

CONCLUSION

1. Both vitamin D supplementation in form of monthly injections as well as non-supplementation and just counselling for increasing dietary intake can lead to increment in vitamin serological level at the end of pregnancy, though being higher in the supplemented group.

2. There is no difference in the incidence of clinical complaints between pregnants receiving the monthly supplementation and that kept on just counselling without supplementation and the supplementation is not risky for adverse effect development.

3. Urolithiasis was encountered in both supplemented and non-supplemented groups, but vitamin supplementation was associated with a higher incidence and was estimated to be risky for its development.

RECOMMENDATION

1. For attaining the proposed benefits of vitamin D supplementation during pregnancy, we recommend adopting the regimen of monthly supplementation three times in pregnancy as it seems to be a feasible way that is associated with a better improvement of the serological level at end of pregnancy than just keeping patients on mere counselling for increased dietary intake and without a higher risk of clinical complaints.

2. Taking precaution against factors enhancing urolithiasis during vitamin administration until further studies on a larger sample are done searching for the statistical significance of the results in our study suggesting this relationship.

REFERENCES

[1] O'Riordan MN, Kiely M, Higgins JR, Cashman KD. Prevalence of suboptimal vitamin D status during pregnancy. Irish Medical Journal 2008; 101(8):240, 242-3.

[2] Sloka S, Stokes J, Randell E, Newhook LA, Seasonal variation of maternal serum vitamin D in Newfoundland and Labrador. Journal of Obstetrics and Gynaecology Canada: JOGC 2009;31(4):313-21.

[3] Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? Journal of Steroid Biochemistry and Molecular Biology 2014;144(Pt A): 138 -45.

[4] Nicolaidou P, Hatzistamatiou Z, Papadopoulou A, Kaleyias J, Floropoulou E, Lagona E, et al. Low vitamin D status in mother-newborn pairs in Greece, Calcified Tissue International 2006;78(6):337-42.

[5] Moller UK, Streym S, Mosekilde L, Heickendorff L, Flyvbjerg A. Frystyk f. et al. Changes in calcitropic hormones, bone markers and insulin-like growth factor I (IGF -I) during pregnancy and postpartum: a controlled cohort study. Osteoporosis International 2013;24(4): 1307-20.
[6] Pludowski P, Holick MF, Pilz S. Wagner CL, Hollis BW, Grant WB. et al, Vitamin D effects on musculoskeletal health, immunity; autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Auto immunity Reviews 2013; 12(10): 976-89,
[7] Cochrane De-Regil. Vit D supplementation ior women dy.ri.ng pregnancy. The Cochrane Library. 2016 (online library. wiley.com).
[8] NICE guidelines, (ANC of uncomplicated pregnancy: nutritional supplements during pregnancy), 2008,.
[9] Myoclinic. Myoclinic-Drugs & supplements. **(**http://www.mayoclinic.org/drugs-supplements/ Vitamin D) **(**website article)
[10] RHL: The WHO Reproductive health Library. Vit D supplementation during pregnancy. (website article).
[11] Viamin D Counsil. Newsletter: vitamin D & kidney stones. (website article).
[12] Endocrine society's 94 Annual meeting & Expo, Tx: Meeting Abstract-Endocrine Society Journals publications). June 23-26, 2012.
[13] Medline. Dietary factors & the risk of incident kidney stones in men: new insights after 4 years follow up [PubMed- indexed for Medline].
[14] Folger GK. Pain and pregnancy; treatment of painful states complicating pregnancy, with particular emphasis on urinary calculi. Obstet Gynecol, J955 Apr. 5 (4);513-8.
[15] Rodriguez PN, Klein AS. Management of urolithiasis during,. Surg Gynecol Obstet. 1988 Feb. 166(2): 103-6.
[16] Destedt JD, Razvi H. Management of urinary calculi during pregnancy. JUrol 1992 Sep; 148 (3pt): 1072-4; discussion 1074-5 [Medline].
[17] Stacie Nguyen, Leo Bagged y. Christine French, Robert P. Heaney, Edward D. Gorham, Cedric F. Garland. 2,5 -Hydroxyvitamin D in the Range of 20 to 100 ng/mL and Incidence of Kidney Stones, American Journal of Public Health, 2013; el DOl: 1 0.2 105/AJPH.201 3.30 1368)
[18] Institute of Medicine Food, Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington DC; National Academy Press, 2010,
[19] Jones G. Pharmacokinetics of vitamin D toxicity. American Journal of Clinical
[20] Lankes U, Elder PA, Lewis JG, George P. Differential extraction of endogenous and exogenous 25-OH-vitamin D from serum makes the accurate quantification in liquid chromatography - tandem mass spectrometry assays challenging, Annals of Clinical Biochemistry 20I5;52(Pt 1):151-60.
[21] Biyani CS, Joyce AD. Urolithiasis in pregnancy management. BJU Int. 2002 May,89:(8);8I9-23.
[22] Medscape, Obs and Gyne, pregnancy and urolithiasis, background. (website article).