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The Effect of Vitamin D and Calcium plus Vitamin D during Pregnancy on Pregnancy and Birth Outcomes: a Randomized Controlled Trial

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ABSTRACT

Introduction: Evidence suggests a high prevalence of calcium and vitamin D deficiencies exists in both pregnant women and babies. Adequate intake of micronutrients has great importance especially during pregnancy and lactation period. Thus, the present study aimed at assessing the effect of vitamin D and calcium-vitamin D on pregnancy and birth outcomes (including duration of pregnancy, type of delivery and infant anthropometric indicators).

Methods: A randomized, controlled, clinical, triple-blind trial conducted on 126 pregnant women referring to Tabriz health centers in 2013-14. Subjects were allocated into three groups using block randomization. Interventional groups received vitamin D, calcium-vitamin D and placebo pills daily for 60 days. ANCOVA and Chi-square tests were used for data analysis.

Results: By controlling BMI before and during pregnancy, there were no significant differences between the group in average neonatal weight, height and head circumference, duration of pregnancy, type of delivery and gestational age at the time of delivery.

Conclusion: The results show that calcium-vitamin D and vitamin D have no effect on duration of pregnancy, type of delivery and infant anthropometric indicators.

Introduction

Recent evidence indicates a role of maternal diet during pregnancy on different birth outcomes such as length of gestation and fetal growth.[1] An adequate intake of micronutrients in mothers, especially during pregnancy and breastfeeding, is very important.[1] Calcium is an essential nutrient,[2] and improves metabolic function, bone health, and neuromuscular function.[3] The total concentration of calcium reduces during pregnancy, because of increases in plasma volume, increased glomerular filtration, and maternal-fetal calcium transport. Calcium and vitamin D deficiency is very common in pregnant women and infants[4,5] and is an epidemic phenomenon worldwide.[6] The prevalence of vitamin D deficiency have been reported as 50-71% during pregnancy and 15-65% in infants.[7,8] In an Iranian study, the prevalence of vitamin D deficiency in pregnant women and infants have been reported respectively as 86% and 75% during winter and 46% and 35% during summer.[9] It seems that vitamin D deficiency is a serious problem during pregnancy. So, considering this problem can be effective in prevention of vitamin D deficiency in mothers and infants.[10]

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Growing fetus imposes a considerable burden on mother homeostasis of calcium. During pregnancy, the fetus obtains about 30 grams of calcium and 80% of it deposited in fetus bones in the third trimester of pregnancy. This need is met mainly by increasing intestinal calcium absorption by the intestines of mother that mediated by 1, 25-dihydroxyvitamin D_3. During pregnancy calcium needed for fetal development and lactation may be at least partially withdrawn from the mother's skeleton. So, adequate intake of calcium to prevent excessive depletion of calcium from the mother's body is necessary.[11] If there is no enough calcium in the mother's diet, the risk of pregnancy complications may increase.[12]

Some previous studies showed the relationship between consuming calcium supplementation and preterm delivery,[13] infant and maternal mortality,[14] improvement of maternal weight gain during pregnancy,[10] and also improvement in neonate Apgar score in the first minute after birth.[15] The effect of calcium intake on the growth of infants is unknown.[12] In some studies, calcium supplements cause better weight gain in infants.[10] However, other studies showed no effect for this supplement.[16] It has been reported that calcium intake during pregnancy leads to elevated serum levels of vitamin D and folate in mothers and also increases bone density[17] and size of bone[8] in infants. Calcium supplementation may reduce the incidence of pregnancy induced hypertension and pre-eclampsia.[18]

Vitamin D supplementation during pregnancy was suggested as a treatment for protection against adverse pregnancy outcomes.[19] According to a systematic review, the association between vitamin D levels and pregnancy outcomes including preeclampsia, gestational diabetes, preterm birth, cesarean delivery, and low birth weight is conflicting.[20] In some studies, vitamin D supplementation reduced the rate of cesarean delivery[21] and in others such effects were not reported.[16] Also vitamin D supplementation during pregnancy increased the birth weight and in others such effects was not reported.[22,23]

Vitamin D deficiency during pregnancy can be associated with many short and long term problems in neonates such as recurrent wheezing,[24] rickets in children,[7] type one diabete,[25] multiple sclerosis,[26] weakness of internal immune system,[27,28] vitamin D deficiency in infants,[29] and smallness for gestational age (SGA).[30] According to previous studies, using supplements during pregnancy is necessary to increase the serum levels of calcium and vitamin D in mothers and neonates.[5] Recently, the American College of Obstetricians and Gynecologists suggested taking 600 IU of vitamin D daily during pregnancy to support fetal and maternal bone metabolism.[20]

Therefore, due to lack of the final conclusions from previous studies, suggestion of more clinical trials to determine the exact effect of vitamin D supplementation on pregnancy outcomes in a systematic review conducted by Urrutia and Thorp, limited amount of vitamin D in dietary regime, and good patient compliance to taking vitamins, the aim of present study was to examine the effects of vitamin D and calcium-vitamin D supplements on anthropometric indices of neonates and mode of delivery in pregnant women.[3,20]

Materials and methods

This study is a randomized, controlled, clinical, triple blind trial that carried out on 18 to 39 years pregnant women with gestational age of 25 to 30 weeks in Tabriz health centers in 2013. Exclusion criteria were: History of chronic diseases (diabetes, heart disorders, etc.), kidney problems (including kidney stones, etc), osteomalacia, active thyroid or parathyroid diseases, endocrine disorders, hypertension, use of diuretics, calcium-blockers intake, chronic hypertension, and history of allergy to the study supplements.

According to a study by Saboor et al.,[10] and by considering $\alpha = 0.05$, $\beta = 0.15$, $m_1 = 49.5$ cm (mean weight of neonates before intervention), and $m_2 = 51.9$ cm and by proposing 5% increase in mean of height after intervention, $sd_2 = sd_1 = 3.8$, the sample size for each group was calculated for 37 women. This number was increased to 42 women by considering the probability of sample attrition.

The study instruments included demographic and obstetric checklists and checklist for recording mothers' (duration of pregnancy and mode of delivery) and neonates' (weight, height and head circumstances) information. To determine the validity of instruments, content validity was used. So, the questionnaires and checklists were given to faculty members and after collecting their comments, necessary modifications were made based on their feedbacks.

With the purpose of sampling from 80 health centers, centers with more number of referring women were selected. In addition, an attempt made to choose the centers that represent different socio-cultural status of Tabriz until the sample size was achieved. In the selected centers, the subjects were selected by convenience sampling method. In this regard, pregnant women with gestational age of 25 to 30 weeks were selected by reviewing their health records and invited to participate via telephone call. After explaining the study objectives and methods, written informed consent was obtained from all participants.

Participants were assigned into three groups via block randomization with a block size of three and six with allocation ratio of 1:1:1. These groups were included: intervention groups (calcium-vitamin D and vitamin D groups) and control group (placebo group). Calcium-vitamin D group received 300 mg carbonate calcium plus 1000 unit of vitamin D supplements; vitamin D group received 1000 unit of vitamin D supplements; and placebo group were provided tablets with similar shape, size, and weight. For uniformity of the weight of tablets an inert material was added to tablets of vitamin D group.

To determine the dose of drugs in supplements, one systematic review[30] that reviewed the studies regarding use of calcium supplement in prevention and treatment of hypertension and mothers' and neonates' outcomes was used.

For allocation concealment, drugs and placebo were placed in the same closed opaque envelopes that serial numbered according to allocation sequence. Block scheduling and preparing envelopes were performed by a person not involved in the sampling and data analysis. All women received a daily tablet for 60 days.

Before intervention, demographic and obstetric checklists were completed by all participants. Then, participants were given an envelope containing the supplements. Afterwards, at weeks 2, 4 and 6 participants received phone calls for emphasis on regular use of supplements. After delivery, in order to compare the mean scores, the mother was telephoned about birth outcomes including gestational age, mode of delivery, and neonatal anthropometric measurements (weight, height, and head circumference at birth) which listed on neonates' health cards. The normal range of weight, height, and head circumstance at birth was considered as 2500 to 4000 gram, 45 to 55 cm, and 33 to 37 cm respectively.[31]

Data were analyzed using the Statistical Package for Social Sciences SPSS version 13. The normality of quantitative variables was analyzed using K-S normality test. Accordingly, weight, height, head circumference, and gestational age were normal. To compare the groups about some demographic characteristics one-way ANOVA, chi-square, trend chi-square, and exact Fisher tests were used. Also, ANCOVA test was used with control of pre-pregnancy and during pregnancy BMI for comparison weight, height, head circumference, and

gestational age among groups. In addition, chi-squire test was used for comparison the mode of delivery among groups.

Results

In this study, 126 pregnant women referred to Tabriz health centers, were enrolled from June to December in 2013 and the follow-up continued until April 2014. The neonate anthropometric characteristics of 2 women in calcium-vitamin D group were not available.

Therefore, in this study, 124 pregnant women were in 3 groups including: 40 women in the calcium-vitamin D group, 42 women in vitamin D group, and 42 women in control group. Over half of participants had a diploma degree (56%). 85%, 96%, and 48% of participants consumed multivitamin, iron, and calcium supplements respectively.

There were no statistical differences between groups regarding consuming of foods containing calcium and vitamin D during one week before intervention (P= 0.204) and demographic characteristics (P> 0.05) in spite of pre-pregnancy BMI (P= 0.024) and BMI during pregnancy (P= 0.008). The mean age of participants was 27.2 years (SD = 5.2) and the number of previous deliveries was 1.6 (SD= 0.7). The majority of patients were housewives (94%) (Table1).

The average birth weight of three groups was: 3225.6 gram (SD=473.3) for the group receiving calcium-vitamin D, 3150.2 gram (SD= 325.8) for the group receiving vitamin D, and 3192.1 gram (SD=392.4) for the placebo group. The results of statistical analysis by ANCOVA test with adjusting based on BMI before and during pregnancy included: there was no statistical difference between group receiving calcium- vitamin D and control group [adjusted difference=-22.8; confidence interval=-198.4 to 152.7]; between group receiving vitamin D and control group [adjusted difference=-87.4; confidence interval=-259.7 to 84.8]; between group receiving calcium-vitamin D and group receiving vitamin D [adjusted difference= 64.5; confidence interval = -107.6 to 236.7] (P= 0.579) (Table 1).

The average height of three groups after intervention was: 50.0 cm (SD= 2.2) for the group receiving calcium-vitamin D, 49.8 cm (SD= 1.9) for the group receiving vitamin D, and 49.5 cm (SD= 2.0) for the placebo group.

The results of statistical analysis by ANCOVA test with adjusting based on BMI before and during pregnancy included: there was no statistical difference between group receiving calcium-vitamin D and control group [adjusted difference=0.2; confidence interval=-0.6 to 1.1]; between group receiving vitamin D and control group [adjusted difference=0.1; confidence interval= -0.7 to 1.0]; between group receiving calcium-vitamin D and group receiving vitamin D [adjusted difference= 0.1; confidence interval = -0.7 to 1.0] (P= 0.841) (Table 1).

The average head circumstance of three groups after intervention was: 34.9 cm (SD = 1.4) for the group receiving calcium-vitamin D, 34.8 cm (SD = 1.3) for the group receiving vitamin D, and 34.8 cm (SD = 1.4) for the placebo group. The results of statistical analysis by ANCOVA test with adjusting based on BMI before and during pregnancy included : there was no statistical difference between group receiving calcium-vitamin D and control group [adjusted difference= 0.07; confidence interval=-0.5 to 0.7]; between group receiving vitamin D and control group [adjusted difference= -0.06; confidence interval=-0.6 to 0.5]; between group receiving calcium-vitamin D and group receiving vitamin D [adjusted difference= 0.1; confidence interval= -0.4 to 0.7] (P= 0.911) (Table 2).

The average gestational age of three groups at delivery was: 272.4 day (SD= 11.7) for the group receiving calcium-vitamin D, 274.2 day (SD= 9.4) for the group receiving vitamin D, and 273.6 cm (SD= 10.5) for the placebo group. The results of statistical analysis by ANCOVA test with adjusting based on BMI before and during pregnancy included : there was no statistical difference

between group receiving calcium-vitamin D and control group [adjusted difference= -1.5; confidence interval= -6.2 to 3.2]; between group receiving vitamin D and control group [adjusted difference= -0.2; confidence interval= -4.4 to 4.9]; between group receiving calcium-vitamin D and group receiving vitamin D [adjusted difference= -1.7; confidence interval= -6.4 to 2.9] (P= 0.722) (Table 2).

28 women (66.7%) in the group receiving calcium-vitamin D, 30 women (71.4%) in the group receiving vitamin D, and 26 women (61.9%) in the placebo group had a cesarean delivery. According to chi-square statistical test, there was no significant difference between groups regarding mode of delivery (P = 0.436). The reason for cesarean delivery in over one third of women (34.1%) was a history of previous cesarean delivery or elective cesarean delivery (Table 3).

3 women (7.1%) in the group receiving calcium-vitamin D, 2 women (4.8%) in the group receiving vitamin D, and 4 women (9.5%) in the placebo group had a preterm delivery. According to chi-square statistical test, there was no significant difference between groups regarding preterm delivery (P = 0.908) (Table 3).

Table1. Demographic and obstetrical characteristics of the participants and their newborns characteristics by study groups

Characteristics	Calcium-vitamin D n=42	Vitamin D n=42	Placebo n=42	P
Age (years)				0.759†
< 20	4 (9.5)	4 (9.5)	3 (7.1)	
20-30	26 (61.9)	23 (54.8)	29 (69.0)	
> 30	12 (28.6)	15 (35/7)	10 (23.8)	
Mean (SD)***	27.5 (5.3)	27.7 (5.6)	26.4 (4.9)	0.509*
Education				0.487***
Primary and secondary school	8 (19.0)	5 (11.9)	6 (14.3)	
High school	6 (14.3)	3 (7.1)	5 (11.9)	
Diploma	22 (52.5)	25 (59.5)	23 (54.8)	
University	6 (14.3)	9 (21.4)	8 (19.0)	
Housewife	41 (97.6)	39 (92.9)	39 (92.9)	0.698¥
Economy status				0.851***
Adequate	8 (19.0)	10 (23.8)	8 (19.0)	
Relatively Adequate	28 (66.7)	25 (59.5)	30 (71.4)	
Inadequate	6 (14.3)	7 (16.7)	4 (9.5)	
Parity				0.594¥
1	15 (35.7)	20 (47.6)	21 (50.0)	
2	19 (45.2)	17 (40.5)	17 (40.5)	
>3	8 (19.0)	5 (11.9)	4 (9.5)	
Mean (SD)**	1.8 (0.8)	1.6 (0.7)	1.6 (0.7)	0.321*
Body mass index (kg/m^2)Mean (SD)**	25.0 (3.8)	25.1 (4.4)	23.0 (4.5)	0.048*
Having an interest in pregnancy	38 (90.5)	39 (92.9)	34 (81.0)	0.204¥
Multivitamin supplementation in pregnancy	35 (83.3)	38 (90.5)	34 (81.0)	0.473†
Iron supplementation in pregnancy	42 (100)	41 (97.6)	38 (90.5)	0.066†
Calcium supplementation in pregnancy	20 (47.6)	22 (52.4)	18 (42.9)	0.158†

Data indicate number (%), except they have been reported with other names, †Fisher's Exact Test,*One way ANOVA, **mean (standard deviation), ***Linear-by-Linear Association, ¥ Chi-Square,

Table 2. Comparison of the average scores of anthropometric indices and gestational age in three groups of calcium-vitamin D, vitamin D and placebo

Groups	Birth weight (kg) * Mean (SD)†	Birth Height (cm)* Mean (SD)†	Head circumference at birth (cm)* Mean (SD)†	Duration of pregnancy (days)* Mean (SD)†
Calcium-vitamin D	3225.6 (473.3)	50.0 (2.2)	34.9 (1.4)	272.4 (11.7)
Vitamin D	3150.2 (325.8)	49.8 (1.9)	34.8 (1.3)	274.2 (9.4)
Placebo	3192.1 (392.4)	49.5 (2.0)	34.8 (1.4)	273.6 (10.5)
Group comparison	**MD (95% CI)‡**	**MD (95% CI)‡**	**MD (95% CI)‡**	**MD (95% CI)‡**
Calcium-vitamin D with control	-22.8 (-198.4, 152.7)¥	0.2 (-0.6, 1.1)¥	0.07 (-0.5, 0.7)¥	-1.5 (-6.2, 3.2)¥
Vitamin D with control	-87.4 (-259.7, 84.8)¥	0.1 (-0.7, 1.0)¥	-0.06 (-0.6, 0.5)¥	0.2 (-4.4, 4.9)¥
Calcium-vitamin D with control	64.5 (-107.6, 236.7)¥	0.1 (-0.7, 1.0) ¥	0.1 (-0.4, 0.7)¥	-1.7 (-6.4, 2.9)¥

*ANCOVA with controlling BMI before and during pregnancy, † Mean (Standard Deviation), ‡Mean Difference (95% Confidence Interval), ¥ P<0.05

Table 3. Comparison of the mode of delivery, cause of cesarean section and type of delivery according gestational age in three groups of calcium-vitamin D, vitamin D and placebo

Variable	Calcium-vitamin D n=42	Vitamin D n=42	Placebo n=42	P
Mode of delivery				P=0.436†
NVD	14 (33.03)	12 (28.6)	16 (38.1)	
CS	28 (66.7)	30 (71.4)	26 (61.9)	
Causes of CS*				P=0.216†
Elective	4 (9.5)	10 (23.8)	5 (11.9)	
Previous cesarean	5 (11.9)	9 (21.4)	10 (23.8)	
Other	17 (40.5)	11 (26.2)	13 (31.0)	
Gestational age at delivery (weeks)†				P=0.908†
Term (≥37)	38 (90.5)	40 (95.2)	38 (90.5)	
Preterm (<37)	4 (9.5)	2 (4.8)	4 (9.5)	

Numbers (percents) have been reported, † Fisher's exact test, *Cesarean section

Discussion

The prevalence of vitamin D deficiency has increased in many countries.[7-9] Also, due to the increased needs of the fetus to maternal resources; supplementation is recommended for pregnant women.[32,33] The findings of this study indicate that vitamin D and calcium-vitamin D supplementation during pregnancy were not improved anthropometric indices (weight, height, and head circumference). According to Mallet et al., study that conducted on 77 pregnant women, significant differences were not found in birth weight in the group receiving vitamin D suplements.[34] These findings are consistent with the findings of the present study. Other studies with different dose of these supplements are needed to investigate the possible effects of such supplementation. In an obsevational study by Ortega et al., reported no significant differences between groups in term of birth weight increasing and increasing daily calcium intake in pregnant women.[16] The findings of this study are consistent with the results of present study.

Saboor et al., in their cross-sectional study on 449 pregnant women found a positive relationship between maternal calcium intake and maternal indicators (weight gain) and infants (weight, height, and one minute

Apgar) anthropometrics indicators. But, there was no effect on the head circumestance.[10] The results of this study are different with our results about neonatal weight and height. So, future studies with larger sample size to assess blood levels of vitamin D and calcium are necessary.

In other study by Karandish et al., intake of 1 gram calcium per day by pregnant women increased birth weight but had no effect on height and head circumference of neonates.[2] The results of this study are consistent with these results regarding height and head circumference. Also, the study by Niromanesh et al., showed that intake of 2 grams calcium supplement daily increased 552 grams of birth weight.[35] The findings of this study are inconsistent with the results of present study regarding weight. Possible reasons for these differences can be the different doses of the supplements used in these studies.

Purwar et al., conducted a study on 201 pregnant women who recieved 2 grams daily calcium from 20 weeks after gestation and found no increase in birth weight of neonates.[36] The findings of this study are inconsistent with present study. Possible explanation for this inconsistency is higher dose of calcium in this study and administration of supplement in lower gestational age.

According to the results of another study by Hollis et al., birth weight, mode of delivery, and duration of pregnancy were not different in pregnant women who received three doses of vitamin D.[22] The findings of this study are consistent with the results of present study.

The results of these studies suggest that regarding the effects of vitamin D and calcium-vitamin D supplementation during pregnancy on improvement of anthropometric indices of neonates (weight, height, and head circumference) is extremely contradictory and other clinical trials in this area are needed.

Merewood et al., reported that vitamin D deficiency increases the rate of cesarean delivery.[21]

This result is not consistent with the results of present study. The possible explanation for this finding is that over one third (34.1%) of caesarian deliveries in present study were due to previous caesarian surgery or elective caesarian delivery. According to case-control study by Baker et al., vitamin D deficiency in first trimester of pregnancy has no association with premature birth.[37] Also, Thorp et al., in another case-control study reported that in women with previous history of premature birth; the vitamin D status in mid-pregnancy had no association with recurrence of preterm birth.[38] Results of this study have an association with the results of present study.

One limitation of this study was lack of measurement of serum level of calcium and vitamin D. So, it is recommended that studies should be done by measuring the level of these supplements. Also, there is a need for future studies on people with calcium and vitamin D deficiencies in order to examine the impact of such supplementations. Studies that compare neonatal anthropometric parameters in women with low levels of these supplements with other women without such deficiencies are needed. The main objective of this study is to investigate the real effects of these supplements.

Conclusion

The results of this study indicate using 1000 IU vitamin D or 300 mg calcium carbonate plus 1,000 IU of vitamin D daily for 8 weeks have no significant effects on infant anthropometric indices (weight, height, and head circumference), gestational age, mode of delivery based on gestational age. Future clinical trials should investigate the impact of vitamin D and calcium-vitamin D supplementation with different doses. Also, it is better that supplementation begin on

lower gestational age with greater sample size and longer follow-up. Such studies are necessary for more accurate conclusions in this area.

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Ethical issues

None to be declared.

Conflict of interest

The authors declare no conflict of interest in this study.

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