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Effectiveness of maternal vitamin D supplementation on maternal and fetal outcomes among antenatal mothers: A systematic review

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***Abstract*---**Vitamin D is a fat-soluble lipophilic prohormone. Vitamin D is synthesized in human body inresponse to UV light. The significance of vitamin D have been documented in a large number of experimental researches that support relationship between vitamin D status and human health. The chief identified impacts of vitamin D on human body is bone health, pregnant women health, foetal health, mineral homeostasis, anti-inflammatory etc. Aim of the present review is to summarize the impact of maternal vitamin D supplementation on maternal-fetal outcomes, to identify the most commonly used tools for measuring maternal vitamin D supplementation, and report on the maternal and foetal outcomes of maternal vitamin D supplementation. The deficiency of Vitamin D in pregnant women and neonates is a common problem that affects people all over the world. The preterm birth risk is increased by 60% in pregnant mothers when the maternal 25-OH-D concentration is less than 40 µg/ml. The research articles consider for the present systemic review meet the following criteria: (i) A non-intervention, intervention and quantitative research studies to look at the effects of maternal vitamin D supplementation on maternal and foetal outcomes, and (ii) the article was published in peer-reviewed journals. During literature survey, there are six empirical studies were identified to be relevant to the search investigation. The Vitamin D supplement at various dosage levels is considered for this review. When comparing the vitamin D insufficiency group to the

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normal vitamin D group, we discovered that babies with low birth weight was more likely to be vitamin D deficient. While studying the literature, we noticed that the higher maternal 25(OH) D concentrations were associated with a lower risk of low birth weight, small size for gestational age and preterm birth across the entire range at P< 0.05. In view of that present systemic review is aimed to discuss about the significance of vitamin D supplementation and its impact on pregnant women and foetal outcome.

***Keywords*---**vitamin D deficiency, maternal outcome, fetal outcome, antenatal mother.

Introduction

Vitamin D is a group of fat-soluble lipophilic secosteroid. Vitamin D is broadly classified into two different groups namely vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). When the human skin is exposed to sun light (UV radiation), the lower epidermal layer of the skin abundantly synthesis cholecalciferol (D_3) (Karras et al., 2016). However human can intake vitamins D_2 and D_3 through their diet and food supplements. The food materials such as fish flesh, fish oil, dietary supplements, egg yolk, butter, liver, fortified foods, mushrooms (grown in UV light) etc., naturally contain significant quantity of vitamin D (Larque et al., 2018). Vitamin D is responsible for increasing intestinal absorption of magnesium, phosphate, calcium and many other metabolic activities. Deficiency of Vitamin D in pregnant women and neonates is a common condition that affects people all over the world (Larque et al., 2018). This deficiency is found in 60% of pregnant women and 14–64% of newborns (Elmee & Shahrokh Taghavi, 2017). During pregnancy, there are significant alterations in calcium and phosphate metabolism, causing calcium to accumulate in the fetal skeleton (Curtis et al., 2018). In the time of the early stages of pregnancy, there is a steady rise in 1,25-dihydroxyvitamin D [1,25(OH)2D] levels and it has been shown to satisfy the higher fetal calcium demands for adequate bone mineral formation (Karras et al., 2016). A low level vitamin D concentration during the early stage of pregnancy is pave the way for less bone mineral content in the fetal skeleton (Lawlor et al., 2013). Whereas the deficiency of vitamin D in pregnant mother is leads to the increased risk of preeclampsia, caesarean delivery, low birth weight, newborn hypocalcaemia crisis, poor skeletal development, glucose intolerance and immune system dysfunction in both mother and new born. A prenatal check-up can result in foetal growth retardation if a pregnant woman is deficient in vitamin D (Lo et al., 2019). According to the US Institute of Medicine, it has been claimed that 1,000–1,600 IU (25–40 g/day) of supplementary vitamin D is required to obtain the greatest level of vitamin D3 in the body (Singh et al., 2021). The maternal vitamin D level decreased less than 40 µg/ml which is increases (60%) the risk of preterm birth in pregnant mothers (Masoumeh Ghafarzadeh et al., 2021).

Materials and Methods

Study selection and data collection processes

An extensive search of online databases such as PubMed, Psyc INFO, CINAHL and Web of Science were performed as part of a systematic review examining the impact of maternal vitamin D supplementation on maternal and foetal outcomes. In all database searches, the free-text terms "vitamin D supplementation" AND "maternal" OR "foetal" AND "antenatal" were utilized. In the first phase, duplicate articles were removed, and reference lists of relevant publications were searched for fresh research that fulfilled the inclusion requirements. Following the first literature search, reviewers examined titles and abstracts to locate those that fulfilled the selection criteria.

Eligibility criteria

The research articles included in this review meet the following criteria: (i) A non-intervention or randomized study to look at the effects of maternal vitamin D supplementation on maternal and foetal outcomes, (ii) an intervention study to look at the effect of maternal vitamin D supplementation on maternal and foetal outcomes, (iii) quantitative research to look at the effect of maternal vitamin D supplementation on maternal and fetal outcomes, and (iv) the original research articles were published in peer-reviewed journals. The articles are not considered for this work are: case series, case reports, qualitative studies, review articles, thesis, dissertations and the articles are published in other than English language.

Data extraction

Data for the present review retrieved from the previous research articles published earlier. The following data were extracted for the present study are: (i) Study characteristics, year, authors, type of study and country of the data collection, (ii) maternal age, gestational age, & vitamin dose characteristics, and (iii) findings.

Study quality assessment

The quality of the studies are assessed using the following tools: (1) the STROBE reporting requirements for the observational research, (2) the critical review form quantitative research. Complete (score=2), partial (score=1), and imprecise (score=0) responses were possible for each question. For each study, a total score was generated. Based on the results collected, studies are rated as bad (total score less than 12 points), fair (total score 13 to 24 points), good (total score 25 to 30 points), or exceptional (total score 30 to 36 points). Third-party reviewers reviewed the studies independently.

Results and Discussion

Our search approach showed up 353 studies (140 in PubMed, 112 in PsycINFO, 80 in Web of Science, and 21 in CINAHL). We identified 218 suitable articles after

eliminating duplicate publications. The abstracts and titles of all identified studies were checked during the screening step. As a result, 135 studies were excluded from the review because they were deemed unsuitable. As a result, 39 research articles were chosen for the study. 14 studies were eliminated because of the reason they did not match the criteria for selection. Finally, a six empirical studies were found to be relevant to our investigation. (Table 1).

Study quality

The quality rating for the study was "fair" for two studies (Masoumeh Ghafarzadeh et al, 2021; Nageshu et al, 2016) and "good" for the remaining four studies (Singh et al, 2021; Dipali Prasad et al, 2018; Miliku et al, 2016; Hanieh et al, 2014)

Study characteristics

The important methodological features and the general characteristics of all the reviewed studies were summarized in Table 1. The Two cross-sectional studies were (Dipali Prasad et al., 2018; Nageshu et al., 2016), two cohort studies were (Miliku et al., 2016; Hanieh et al., 2014), One was descriptive-analytical study (Masoumeh Ghafarzadeh et al., 2021) and remaining one was the randomized study (Singh et al., 2021) From 2014 to 2021, all of the studies were published. These studies were undertaken in Iran, the Netherlands, India, and Vietnam, among other places.Table1:

Table 1
Participant characteristics

Author (year)	Type of study design (Nation)	Maternal age (Mean ±SD)	Gestational age (weeks)	vitamin D dose	Findings
Masoumeh Ghafarzadeh et al., (2021)	descriptive-analytical study (Iran)	28±7	39	Use supplement vitamin D (4000IU)	only 7 mothers and their infant had sufficient levels of vitamin D.
Singh et al., (2021)	randomized study (India)	20.3±6.1	47	Use supplement vitamin D (60,000 IU)	Vitamin D deficiency group (13.33 percent), low birth weight foetus was more common than in the normal vitamin D group (6.67 percent)
Dipali Prasad et al., (2018)	cross-sectional study (India)	22.3±5	36	Use supplement vitamin D (30-100ng/ml)	Preterm labour (39.38 %), PROM (18.17 %), infection (15.14 %), GDM (12.11

					%), Preeclampsia (6.05 %), and preexisting hypertension are among the complications of pregnancy in vitamin D deficient women (9.08 %). In terms of weight infant, live birth in the Vitamin D deficient group was between % kg (13.25 %) and>2.5 kg (13.25 %) (86.75 percent). Apgar score 7 in the deficient group (18.07 percent) and Apgar score >7 in the non-deficient group (81.92 percent).
Nageshu et al., (2016)	cross sectional study (India)	25.2±3	37	Use supplement vitamin D (6000 IU)	There were no difficulties for 92.3 percent of women with normal vitamin D levels, 81.8 percent of mothers with deficient levels, and babies with normal birth weight 84.6 percent of women with normal vitamin D level.
Miliku et al., (2016)	cohort study (Netherlands)	29.7±5.2	23	Use supplement vitamin D (50.0–74.9 nmol/L)	At P<0.05, maternal D_3 level over the whole range were linked to a decreased risk of low birth weight, preterm birth, and small gestational age at birth.
Hanieh et al., (2014)	cohort study (Vietnam)	28±4.6	32	Use supplement	The relationship between head

				vitamin D (400IU)	circumference of an infant at birth and maternal D_3 (MD of 20.35 cm per 25 nmol/L) supplementation is inverse. An increased concentration of vitamin D supplementation (95 percent, CI 20.62 to 20.09) showed an impact on head circumference and preterm infants (49.5 percent).

Characteristics of antenatal mothers

These 6 studies, the ages of antenatal mothers were between 20.3±6.1 to 29.7±5.2 years.

Supplementation used in mothers

This proper dose for vitamin D supplementation is 4000IU which is recorded by Masoumeh Ghafarzadeh et al., (2021). Singh et al., (2021) recommended supplement vitamin D is 60,000 IU. Dipali Prasad et al., (2018) administrated supplement vitamin D in the dose of 30-100ng/ml. Nageshu et al., (2016) administrated supplement vitamin D in the dose of 6000 IU. Miliku et al., (2016) and Hanieh et al, (2014) recommended vitamin D supplement vitamin D in the doses of 50.0–74.9 nmol/L and 400IU respectively.

Vitamin D supplementation on maternal and fetal outcomes

Among selected studies reported that maternal vitamin D supplementation on maternal and fetal outcomes. Masoumeh Ghafarzadeh et al., (2021) identified the mean vitamin D concentration in pregnant mother was 13 µg/ml, whereas foetus had a concentration of 15 µg/ml. It was recorded that there are 89% of mothers and their newborns were vitamin D deficient. The researchers reported that there is a relation between the amount of vitamin D level in serum and umbilical cord. Vitamin D levels in mothers and newborns were unaffected by gestational age, maternal age, body mass index, or work status. The Vitamin D levels were good and increased in women who took vitamin D supplements (4000IU/day). In randomized study, Singh et al., (2021) showed that a vitamin D deficit of less than 20 ng/dL was identified in 90.9 % of the participants. Dipali Prasad et al., (2018) reported that deficiency of Vitamin D was found in 88 pregnant women out of 100 women.

The aim of the present review is to identify the impact of maternal vitamin D supplementation on maternal and foetal outcomes. The evaluated research articles revealed that they met the majority of the needed criteria, including topic relevancy, methodological quality, and analysis of the results, as well as their impact. All researchers well documented that the Vitamin D supplementation has a positive effect on maternal and fetal outcomes. (Masoumeh Ghafarzadeh et al., (2021); Gayam et al., (2020); Thangappah et al., (2019); Nageshu et al., (2016); Taneja et al., (2020); Ajmani et al., (2016); Arora et al., (2018); Miliku et al., (2016)). Furthermore, randomized trials revealed that low birth weight newborns were more likely to be vitamin D deficient (13.44 percent) than those with normal vitamin D levels (6.67 percent) (Singh et al, (2021)). Similarly, Shahgheibi et al., (2016); Shakiba & Iranmanesh (2013); Zhang et al., (2016); Chakhtoura et al., (2016); Nausheen et al., (2021); Karamali et al., (2016); Anderson et al., (2018); Hanieh et al., (2014)) explained the recommendation of vitamin D supplementation in the first and second trimesters of pregnancy was effective in reducing gestational diabetes mellitus and controlling glucose tolerance test. Vitamin D_3 dose > 50,000 IU/month is required during the second and third trimesters of pregnancy for vitamin D-deficient pregnant women in order for their neonates to achieve serum 25(OH)D levels > 20 ng/mL. In addition four studies reported that (Dipali Prasad et al., (2018); Nageshu et al., (2016); Miliku et al., (2016); Hanieh et al., (2014)). The intervention group's neonates had significantly different birth weights, heights, and head circumferences. (Suchitra et al., (2021); Bokharee et al., (2020); Moon et al., (2020); Elmee & Shahrokh Taghavi (2017); Mojibian et al., (2015); Hossain et al., (2014); Hashemipour et al., (2013)). In conclusion the entire literature survey and review clearly indicate that impact of vitamin D supplementation on maternal and foetal outcome of antenatal mothers. In order to discover whether parents' coping techniques change based on their hemophilic children, more study in this area is needed. Despite the fact that qualitative research contributes greatly to the literature in this subject, we explicitly excluded it since its results cannot be scaled up to large groups of patient with the same level of reliability as quantitative research.

Conclusion

The data retrieved from the systemic review exhibited that maternal vitamin D supplementation improves maternal and fetal outcomes in pregnant women. Overall, this review found that taking 50,000 IU of vitamin D every two weeks from the 12^{th} week of pregnancy until delivery reduced the risk of GDM, pre-eclampsia, early labor, low birth weight, and other complications. The anthropometric features of the babies in the supplemented groups were significantly different. In pregnant women with baseline levels of less than 30 ng/ml, vitamin D supplementation of 50,000 IU every two weeks can avoid newborn vitamin D deficiency. This dosage is fully risk-free, with no side effects.

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