Impact of vitamin D deficiency in pregnancy: a review of literature

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Abstract

Background: Vitamin D deficiency is major health problems worldwide. This significant high prevalence of vitamin D deficiency is more obvious among pregnant women than any other human groups. The frequency of vitamin D deficiency among Saudi women ranges approximately from 80% to 100 %. Women with inadequate sun exposure, low financial status, and women with two or more births are more liable to suffer from vitamin D deficiency. The available evidence emphasizes many adverse maternal and birth outcomes with vitamin D deficiency during pregnancy.

Objectives: To highlight the prevalence and risk factors of vitamin D deficiency and to demonstrate the adverse effect of vitamin D deficiency on maternal and birth outcomes, aiming to focus on the importance of prevention and control measures for vitamin D deficiency in pregnant females to prevent adverse outcomes.

Review of literature: The evidence available emphasizes adverse maternal and birth outcomes with vitamin D deficiency during pregnancy. Vitamin D deficiency during pregnancy increases the risk of gestational diabetes mellitus (GDM), preeclampsia and preterm births. For the neonate, this is manifested by poor fetal development and altered neonatal growth that may continue into later life.

Conclusion: Testing high risk pregnant females for 25(OH)D3 levels and dietary supplements of vitamin D for those with vitamin D deficiency should be considered during pregnancy to prevent the adverse outcomes. Health awareness programs targeting the pregnant Saudi women are needed to promote their awareness of this significant problem.

Keywords: Alkaline phosphatase (ALP), gestational diabetes mellitus (GDM) , hypovitaminosis , insufficiency , Parathyroid hormone (PTH) ,Small-for-gestational age (SGA) ,Vitamin D deficiency .

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1 INTRODUCTION

Vitamin D deficiency is major health problems worldwide as it affects billion people around the world [1], [2], [3]. Nearly, 67% of pregnant female in the United States of America have of less than the highest standard vitamin D status [4]. In kingdom of Saudi Arabia (KSA), low serum levels of vitamin D can be believe a popular health problem to all age groups. This problem of hypovitaminosis D is higher among women and children [1]. In different studies the detectable range of vitamin D deficiency In the Saudi women is approximately from 80% to 100% [1], [2].
Vitamin D deficiency is more obvious among pregnant women this significant high prevalence than any other human groups because of the expansion in maternal and fetal vitamin D demands throughout pregnancy [1], [2] .

Vitamin D has important functions in pregnancy including its sequences for glucose homeostasis, placental function, infection and inflammation, and has an important role as well in the manufacture of pro inflammatory cytokines, such as interleukin (IL)-6, interferon-gamma, tumor necrosis factor (TNF)-α [4].

The evidence available emphasizes many adverse maternal and birth outcomes with vitamin D deficiency during pregnancy [1]. The adverse maternal outcome of vitamin D deficiency during pregnancy is the elevation the risk of gestational diabetes mellitus (GDM), preeclampsia and preterm births or small-for-gestational age (SGA) [4]. For the neonate, this is manifested by reduced fetal development and changed neonatal growth that could continue into future life and may result in impaired in development of infant language in school-aged children [5], [3].

Given the general wellbeing significance of clearing up the potential adverse effects of vitamin D deficiency in pregnancy, we conducted this review of literature to highlight the prevalence and risk factors of vitamin D deficiency and to demonstrate the relationship between low maternal vitamin D levels and the maternal and birth outcomes, aiming to bring focus of light on the importance of prevention and control hypovitaminosis D before or early in pregnancy to prevent associated maternal and neonatal related complications [4].

2 OBJECTIVES

1- To identify the prevalence of vitamin D deficiency in pregnant women worldwide and among Saudi women.

2- To demonstrate the risk factor of vitamin D deficiency.

3- To illustrate the effect of lack vitamin D during pregnancy on maternal and neonate outcomes.

4- To high lighten the preventive and control efforts of vitamin D deficiency among pregnant females.

3 REVIEW OF LITERATURE

1.Lack of vitamin D among pregnant females: magnitude of the problem

Vitamin D (calciferol), It is an fundamental fat-soluble vitamin. (1,25(OH)2D) is the active form of vitamin D watches present in the liver and kidney. 25(OH)D is the main circulating vitamin D metabolite and its concentration level of 25(OH)D serum is a biomarker of the vitamin status [2] .
Vitamin D is required for metabolism of the bone, regulation of calcium and phosphate and plays a significant role in neuromuscular functions. Furthermore, it keeps up great wellbeing, also it controls a great amount of human genes (approximately 200 genes), additionally vitamin D is included in another cell function like apoptosis, regulation and cell proliferation. In addition, it applies immune responses through regulation of the innate and adaptive immunity. Receptor of Vitamin D may modulate function and secretion of pancreatic β-cell, as that way affect circulating glucose. It is produced by the body during exposure to sunlight, and is also found some food products like eggs, oily fish and fortified [1], [2], [6].

In all age groups, Vitamin D deficiency is a general medical issue around the world. In a systematic review that collected 18 studies done in Western countries involving first trimester pregnant women, white pregnant women from Caucasian were found to have a mean concentration of 25(OH)D range between 29 - 73 nmol/L. while the mean concentration of 25(OH)D levels were lower in non-Caucasian pregnant women, extending between 15.2 and 43 nmol/L. Similarly, in non-Western countries, the greater proportion of pregnant females who past their first trimester had 25(OH)D levels < 75 nmol/L; these include some countries like India, Pakistan, Turkey and Kuwait. At delivery the worse levels (<25 nmol/L) have been found in the Emirates and Saudi Arabia [7].

Table1 categorizes different cut off levels of vitamin D lack ranging from deficiency (25(OH)D less than 50 nmol/L), insufficiency (25(OH)D ranging from 50–80 nmol/L), up to 325 intoxication. Furthermore, serum 25(OH) concentration < 20 ng/mL are considered severe vitamin D deficiency [8], [9].

Table 1: Cut off levels of 25(OH)D and 25(OH) serum concentrations for vitamin D

25[OH]Level (ng/mL)	25[OH]D Level (nmoL/L)	Laboratory Diagnosis
<20	<50	Deficiency
20-32	50-80	Insufficiency
54-90	135-225	Norm al in sunny countries
>100	>250	Excess
>150	>325	Intoxication

Alshahrani F and Aljohani N (2013) [8]

In Saudi Arabia early reports of vitamin D deficiency in women developed 30 years ago. In initial 1980s the first detected low level of serum 25(OH)D between non-pregnant and pregnant Saudi female [6 ng/ml (range: 2-18 ng/ml)] is published by two epidemiologic studies [1]. In the evaluation of vitamin D levels between pregnant Saudi femeals there is limited studies have been published, Azhar, 2009 investigated the serum 25(OH)D in 118 healthy pregnant and non-pregnant Saudi female from western area. The results discovered that 97.5% of Saudi female (98.6% of non-pregnant female and 95.8% of pregnant female) had 25(OH)D level equal to or lesser than 50 nmol/L, that is show that a great portion of these female have vitamin D deficient [10].

The study complete in KSA by Al-Faris 2016 to detected the prevalence of vitamin D deficiency between pregnant Saudi female in capital city in KSA Riyadh found that more than 90% pregnant women were vitamin D deficient or insufficient [1].
Kanan et al, said Saudi women age less than 30 years had high vitamin D inadequacy matched to those age older than 30 years. This might be because the older women taking more vitamin complements and unhealthy habits of nutritional between younger women distinctive by high junk food utilization [11]. Al-Ajlan et al, 2015 evaluated the serum vitamin D status of 515 healthy pregnant Saudi women in primary trimester, and analyzed its association with gestational diabetes mellitus (GDM). Highly prevalent of Vitamin D deficiency was establish, with only 3.5 % of the women had sufficient levels and a 2.5 % women had needed levels of vitamin D, while the other (94.2 %) were either deficient or insufficient [6].

2.Risk factor of vitamin D deficiency:

In the study counting 92 pregnant women there age from 20 to 40 years, Aly et al, 2017 described women with elevated risk for vitamin D deficiency as those with inadequate exposure to the sun, low financial state and women with two or more births who were generally more likely to have lower 25(OH)D3 concentrations matched to women had adequate exposure to sun, higher level of financial state, and women with only one previous birth (P<0.05) [5]. Same results also mentioned by Merewood et al, 2010 [12]. And Shand et al, 2010 detected Risk factors for newborn vitamin D deficiency involving maternal deficiency (adjusted odds ratio 8.55), and maternal BMI ≥35 (OR: 2.78 [95% CI: 1.18–6.55]) [13].

Many studies investigated the association between vitamin D deficiency and overweight. In KSA obesity and overweight women were reported to be more suspected to be vitamin D deficient, they discovered a firm relationship between vitamin D deficiency and obesity [1]. In KSA 2013 Sadat-Ali et al, found most food which should have vitamin D fortified were either not fortified or include a sum not as much as prescribed by the recommendations set for the marketplace in US [14].

Vitamin D status is normally impacted by some factors, par-

ticularly those that influence the rate of vitamin D synthesis by dermal. in instance latitude, day timing, pollution of air and the season of the year and that affect the quantity radiation of UVB achieving the world's surface and therefore skin [1]. As a matter of fact, lifestyles is the big factors that are related to vitamin D state in Saudi Arabia. KSA have great sunshine, and temperatures during the summer is higher [over 50℃], therefore, Saudi people have limited outside exercises throughout a day. Also lifestyle patterns have changed to sedentary lifestyles. Moreover, a lot of Saudi women wear cover their bodies totally by dark veils, due to cultural and religious causes [1].

3.Adverse effects of vitamin D deficiency during pregnancy

The body experiences several physiological adjustments in pregnancy duo to a unique condition in this period, including alteration in the metabolism of vitamin D. The impact of vitamin D deficiency in pregnant women and neonatal is still under investigation in a lot of the researches [2].

In the study done by Aly Yasser et al 2013, there was a weak inverse relationship between the concentrations of 25(OH)D3 in mother and serum Alkaline phosphatase (ALP) [5]. Brooke et al. which was in agreement who reported increased ALP in Asian individual from the United Kingdom by 20% with serum 25(OH)D3 concentrations less than 25 nmol/L (10 ng/mL), while just 2% of those who had concentrations of serum 25(OH)D3 more than 25 nmol/L had increased ALP [15].

3.1- Vitamin D status and gestational diabetes mellitus

The impact of vitamin D deficiency on the health of pregnant women and newborns is still under investigation in a lot of researches [2] .

Gestational diabetes mellitus (GDM) is defined as first detected of intolerance in glucose during pregnancy, threshold for the diagnosis a fasting plasma glucose level higher than 126 mg/dl (7.0 mmol/l) or a casual plasma glucose more than 200 mg/dl (11.1 mmol/l) [16]. The study done by Al-Shaikh et al 2016, involving pregnant women who had vitamin D deficiency aged from 17 to 47 years old, detected major pregnancy associated adverse effects of vitamin D deficiency. They found that GDM (11.1 %), preeclampsia (0.9 %) and the least were restriction of intrauterine growth and gestational hypertension (1.5% and 1.4 %, respectively). Out of the 19 patients (1.9 %) who had pregestational diabetes, 14 had type-1 diabetes mellitus (1.4 %) and five had type-2 (0.5 %). amazingly, miscarriage history among pregnant women was high (24.5 %) [2].

Maternal vitamin D level might increases the risk of GDM possible mechanisms for that is. First mechanisms, 1,25-dihydroxyvitamin D3 binds with the β-cell receptors of vitamin D and modulates secretion and function of pancreatic β-cell, thus affecting circulating glucose levels. resistance of Insulin and β-cell nonfunction is related to decreasing level of vitamin D. Second mechanisms, vitamin D promotes the manifestation of insulin receptors and stimulates sense of insulin for glucose carrying, thus increasing sensitivity to insulin. Finally, it makes the equilibrium among the extracellular β-cell calcium pools and intracellular β-cell calcium pools, which is major for mediating of insulin intracellular mechanism in insulin-senses tissues [4]

According to the study in KSA 2016, Al-Shaikh at el documented that GDM was found in 7% (CI 95%: 5.29–9.1%) of all pregnancies and that it was the most common adverse effect [2]. In a study in 2007, investigating 741 pregnant women for the linked of vitamin D and gestational diabetes mellitus, There was a significant association between the levels of 25(OH)D in pregnant females and sensitivity to insulin or fasting blood glucose levels detect in 7% of them (CI 95%: 5.29–9.1%). low level of the mean vitamin D was a significant difference between GDM and normal groups (22.97 ± 18.25 vs 16.49 ± 10.44, p = 0.009) [16]. This was also detected by Tsur et al, 2013 who recorded the change from normal glycaemia to high blood glucose in patients with low vitamin D low level of the mean vitamin D < 25 nmol/L (severe vitamin D deficiency) [17].

A meta-analysis in 2012 included 7 observational studies and 2146 participants of 433 women diagnosed with GDM has reported a high level of vitamin D deficiency in pregnant women (>50%) thorough vitamin D deficiency (25(OH)D <50 nmol/l) in pregnant women was significantly related to the happening of GDM (OR 1.61, 95% CI 1.19-2.17; p=0.002) [18]. The same is indicated in a meta-analysis of 20 independent observational studies that detected strong evidence that vitamin D deficiency was related with an elevated risk of GDM [19]. However, some studies detected no association between GDM women with deficient and insufficient vitamin D [2].

3.2- Vitamin D deficiency and Preeclampsia

Worldwide prevalence of preeclampsia among pregnant females ranges from 2 to 17 % [4]. A recent study published in 2017 observed low concentration of maternal 25(OH)D less than 37.5 nmol/L, during early pregnancy was linked with increase in the odds of preeclampsia by 5-fold (adjusted OR, 5.0; 95% CI, 1.7–14.1). Furthermore, neonates born from mothers who has pre-eclampsia were significantly more likely to have poor vitamin D status than neonates of mothers who don't have pre-eclampsia [20]. However, the argument still remains about the association of preeclampsia with vitamin D deficiency [2]. So in early pregnancy Vitamin D supplementation must be survey as preventing preeclampsia and enhancing neonatal health in a safe and effectives [20].

3.3- Vitamin D deficiency and neonatal outcomes

The mean concentrations of serum 25(OH)D found to be significantly lower between the newborn infants of mothers who had a risk factors of vitamin D deficiency, than newborn infants of mothers without risk factors matched to those with one or more risk factor (33.44 ± 18.33 vs 55.39±17.37 nmol/L; P value less than 0.01) [5].

Regarding to the serum biochemical markers of the neonatal, the mean calcium levels were demonstrate to be potently low-

er in newborn infants of mothers who had a risk factors of vitamin D deficiency than those in newborn infants of mothers without risk factors (8.04±0.47 vs 9.07±0.62 mg/DL; P value less than 0.05). Also significantly higher levels of alkaline phosphatase and serum phosphorus were found in newborn infants of mothers who had a risk factors of vitamin D deficiency [5]. It is to be said that infants who born in winter sessions from mother with insufficient sun exposure had low serum of 25(OH)D3 matched to those infants who born in summer [21]. Zeghoud at al, 1997 reported that neonatal serum concentrations of 25(OH)D3 < 30 nmol/L (12 ng/mL) were linked to raised serum alkaline phosphatase and parathyroid hormone (PTH), also they suggest this level as the cutoff for detecting hypovitaminosis D in infant [22].

An association between language impairment and low concentration of maternal vitamin D has earlier been proposed. A cohort study in Australia including a pregnant women and children in age school , informed that women with an antenatal vitamin D concentration fewer than 46 nmol/L increased the risk of having a child with language difficulties at age between 5 to 10 years of age two-fold [23].The observed relationship between infant development and antenatal vitamin D concentration is rational because vitamin D has an essential role in neural cell development and differentiation, antioxidant activity , also has effect in regulation of cytokine and neurotransmitter synthesis, and it is has been suggested that in utero during the last tow trimesters if the neonatal exposure to vitamin D deficiency may disturb the growth progresses of the Perisylvian structures, which are responsible for children language [3].

There is also interest relationship between vitamin D deficiency and autism. Current research propose during pregnancy or early childhood vitamin D deficiency could be a trigger for autism spectrum disorder in infants genetically predisposed to autism, either through its effect on gene regulation, interaction through neuronal function and brain development [3]. however high quality trials are required in this regard.

4. Preventive and control efforts of vitamin D deficiency among pregnant females

The recommendation of the WHO guideline in 2012 that during pregnancy vitamin D supplementation increased maternal concentrations level vitamin D, but the clinical importance of this still unclear [24].

Hollis at el 2011 recommended supplement of vitamin D by 4,000 IU / day in Beginning at 12-16 weeks of gestation, was best in achieving vitamin D deficiency in pregnancy, one month before delivery without increased toxicity risk at various group of women and their neonates [25].

Vitamin D has dietary sources like eggs (contain 20 IU of vitamin D per one egg). Fatty fish like tuna, salmon and sardines supply 200–350 IU of vitamin D per 100 grams. one cup of cereal products approximately 40–50 IU of vitamin D, but a lot of foods do not contain significant amounts of vitamin D to achieve required [1] .

To improve vitamin D supplementation, the new guideline focuses on the effective ways to improve and prevent deficiency in people who are at risk. The recommendations of guideline include [26].

- Increase access to vitamin D supplements and ensure they are containing the prescribed doses and the suggested every day measure of vitamin D for wellbeing. Should also amend existing statute to allow Healthy Start vitamins to be more broadly sold and promote industrialist to sell them direct to pharmacies.
- Routinely testing of individuals for vitamin D status is not required unless they suffer from symptoms of deficiency, at particularly high danger of deficiency, or there is a clinical motivation to do so.
- National activities to increasing awareness about the significance of vitamin D should be developed.

Routine screening for vitamin D deficiency to all pregnant female is not recommended as indicated in the new American Congress of Obstetricians and Gynecologists (ACOG) guidelines [27] .

From the WHO a Cochrane systematic review survey examine is vitamin D supplements unaccompanied or in combining calcium with it , and given additionally different vitamins and minerals to pregnant female can ameliorate the safely outcomes of maternal and newborns . The study confirmed no risk of pre-eclampsia or infant with low birth weight (less than 2500 g) in pregnant women taking vitamin D supplementation associated to pregnant women not taking supplementation or taking a placebo. Pregnant women who receiving vitamin D supplementation unaccompanied had better serum concentrations of 25-hydroxyvitamin D compared with those who are not receiving any supplementation or placebo [28]. To directly determine the harms or benefits of vitamin D supplementation in pregnancy on maternal and infant outcomes There is limited evidence of that. Supplementation of Vitamin D is not routinely recommended to be prescribed to prohibit preeclampsia and its complications during pregnancy [29].

There are two reviews that draw attention on vitamin D supplementation in pregnancy. They reported weak information connecting vitamin D supplementation to a reduced risk of low birth weight but there were lacking information on other pregnancy outcomes. The clinical importance of these reports is still to be determined as the number of high quality trials is fewer to put conclusion [30], [31].

A Cochrane review including 15 randomized controlled trials register 2833 women has investigated whether vitamin D supplementation throughout pregnancy safely enhances the outcomes of maternal and newborns. The results indicated that supplementation of vitamin D in pregnancy enhance the vitamin D concentration in maternal blood and also decreased the risk of born a premature infant (less than 37 weeks of gestation). The risks of hypertension during pregnancy and a infant with a low birthweight (less than 2500 g) have been reduced. But, they found that when vitamin D and calcium are joined,

the preterm birth is becoming higher and information on maternal evidence were not very much detailed [28].

In two trials that included 219 females mentioned that females who get supplementation of vitamin D may have decreasing the risk of preeclampsia comparison who no got intervention or placebo (8.9% versus 15.5%; risk ratio (RR) 0.52; 95% CI 0.25 to 1.05, low quality). Similarly, the gestational diabetes risk among those who taking supplementation of vitamin D was reduced compared to no placebo (RR 0.43; 95% CI 0.05, 3.45) [28]. As for newborns, Three trials that included 477 women suggested that during pregnancy vitamin D supplementation has decreased the risk of preterm birth associated to no intervention or placebo (8.9% versus 15.5%; RR 0.36; 95% CI 0.14 to 0.93, moderate quality). Other results suggested that vitamin D supplementation increases circumference of the head at birth (Mean difference (MD) 0.43, 95% CI 0.03 to 0.83; four trials, 638 women) and infant length (MD 0.70, 95% CI-0.02 to 1.43; four trials, 638 infants) [28]. It is suggested to do routine testing of vitamin D for those of high risk factors during early pregnancy and treatment of those observed to be vitamin D deficient to avoid adverse outcomes [5].

4 CONCLUSION

In pregnant Saudi women vitamin D deficiency is a common health problem. due to its importance of vitamin D in regulating the metabolism of calcium and in maintaining good health more consideration must be given to the status of vitamin D among pregnant women. Routine testing of 25(OH)D3 and dietary supplements of vitamin D early in the pregnancy should be looked for pregnant females at danger of vitamin D deficiency and treatment of those observed to be vitamin D deficient in order to prevent maternal and neonatal adverse outcomes. more research to investigate the impact of longer term supplementation with vitamin on development child and growth and other outcomes is needed. National effective education programs targeting pregnant Saudi females are needed to promote the public education and awareness of this significant problem.

5 Acknowledgment

Great appreciation to the supervisor Dr. Hanan Mosleh (Associate professor of community medicine, Faculty of medicine, Taibah University, KSA) for the help and strict supervision.

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