CURRENT SUPPLEMENTATION RECOMMENDATIONS FOR VITAMIN D INTAKE IN PREGNANCY; WHAT RESEARCH SAYS AFTER 2011

A Paper
Submitted to the Graduate Faculty
of the
North Dakota State University
of Agriculture and Applied Science

By

Kayla Renee Posch

In Partial Fulfillment of the Requirements
for the Degree of
MASTER OF SCIENCE

Major Department:
Health, Nutrition, and Exercise Sciences

November 2017

Fargo, North Dakota

North Dakota State University
Graduate School

Title

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Kayla Renee Posch

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MASTER OF SCIENCE

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Chair: Dr. Yeong Rhee

Dr. Sherri Stastny

Dr. Mark Strand

Approved by Department Chair:

11/13/2017
Date

Dr. Yeong Rhee
Department Chair

ABSTRACT

Vitamin D (vit. D) deficiency is common during pregnancy (Holick, et al., 2011). Supplementation of vit. D has shown to protect against complications and adverse outcomes during pregnancy (De-Regil LM, 2016). A comprehensive literature search and review was conducted to locate articles related to pregnancy outcomes. The literature review found thirteen studies related to vit. D and impact on pregnancy, twenty-five studies examined adverse pregnancy outcomes related to vit. D deficiency and eight studies examined current vit. D intake among pregnant women.

Evidence shows a positive association between vit. D deficiency and pregnancy, suggesting that vit. D sources require closer examination and recommendations for pregnant women and women of childbearing age. Evidence shows mixed results with correlation of vit. D deficiency to adverse pregnancy outcomes. Vitamin D supplementation has shown to contribute to total vit. D intakes and shows adequate increases in serum 25-hydroxyvitamin-D (25(OH)D) levels with supplementation.

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CHAPTER 1. INTRODUCTION

Overview of Topic

The Institute of Medicine (IOM) updated the Dietary Reference Intakes (DRI) in 2010 for vit. D and calcium. This came after the United States (US) and Canadian governments requested a review of recent research and data pertaining to calcium and vit. D requirements. The DRI are established for the public health and the health of the general population living in the U.S. and Canada. More specifically vit. D has been the center of attention in the past 10 years for its possible importance in human health. The relationship of vit. D to several health outcomes has been suggested by researchers in the scientific community, and range from prevention of diabetes and cancer to increased immunity and the reduction of falls among the elderly related to muscle quality. During pregnancy, a low vit. D status can be detrimental to mother and fetus and cause an infant to be vit. D deficient. Maternal vit. D deficiency can lead to pre-eclampsia, cesarean section delivery, gestational diabetes and excess risk for low birth weight for gestational age (Finer, et al., 2012).

In 2010 the IOM committee concluded that skeletal health provided the only contributing outcome for establishing the DRI for calcium and vit. D. There was sufficient dose-response evidence available to meet the criteria as a health outcome indicator and support the development of the DRI. Bone health was then the outcome and basis for the 2011 Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) for those older than 1 year (Ross, et al., 2011).

The American College of Obstetricians and Gynecologist (ACOG) acknowledges that during pregnancy severe vit. D deficiency has been associated with biochemical evidence of disordered skeletal homeostasis, congenital rickets and fractures in newborns. Their opinion is

that evidence is currently insufficient to support routine screening of pregnant women for vit. D deficiency. They do support screening among women thought to be at increased risk of vit. D deficiency, with interpretation of results in the context of the individual clinical circumstances. The ACOG committee opinion is to supplement with 1,000-2,000 IU of vit. D per day, depending on level of deficiency. This amount is safe for consumption among pregnant women (ACOG, 2011). The committee also noted that higher dose regimens have not been studied in pregnancy. Their final recommendations now are to forgo vit. D supplementation among pregnant women beyond what is contained in a prenatal vitamin of 400-600 IU, until more randomized clinical trials are completed. When the opinion of the committee was written in 2011, reaffirmed in 2015, they found that there is insufficient evidence to recommend vit. D supplementation for the prevention of preterm birth or preeclampsia (ACOG, 2011).

The DRI provide recommendations for adequate and safe daily intakes of nutrients that are consumed over many years and possibly over a lifetime. The DRI are a nutrient reference value used by many health practitioners including Registered Dietitian Nutritionists (RDNs). The DRI components include the Estimated Average Requirement (EAR), Recommended Daily Allowance (RDA), Tolerable Upper Intake Level (UL) and the Adequate Intake (AI). The EAR is the average daily requirement for a nutrient. The RDA, which is derived from the EAR, likely meets or exceeds the requirement for 97.5 percent of the population. The UL is the highest average daily intake that will likely pose no risk or adverse effects to most individuals in the general population. The AI, used when the EAR/RDA cannot be developed, is based on observed or experimental intakes. The final DRI indicators for calcium and vit. D were selected based on the strength and quality of the evidence currently available (Table 1) (Institute of Medicine, 2011).

Table 1

IOM vs. ACOG Committee Opinion Recommendations on Vitamin D Intake among Pregnant Women

ACOG Committee Opinion (IU/day)	IOM Recommendations (IU/day)
400-600	600
1,000-2,000 safe upper limit	4,000 upper level intake

(ACOG, 2011) (Institute of Medicine, 2011)

Vitamin D as a nutrient can be synthesized by the human body through the action of sunlight or exogenous sources (e.g. food). This dual component of sun exposure and oral intake made it challenging to establish the DRI values (Institute of Medicine, 2011). Another challenge was using bone health as the basis of establishing the DRI for calcium and vit. D. There is an underlying assumption that the DRI for calcium are reliant on the DRI for vit. D and vis-versa. The requirement for one nutrient assumes that the need for the other nutrient is being fully met. One example the IOM committee gives is when there is inadequacy of one nutrient, this might cause changes in the efficient handling of, or physiological response to the other nutrient that might not otherwise be present. When there is a state of vit. D deficiency with minimal calcium intake, absorption of calcium from the gut cannot be enhanced. In this situation, there is accelerated conversion of 25-hydroxyvitamin D (25(OH)D) to the active form, calcitriol, through an increase in parathyroid hormone (PTH) levels. These types of situations can confuse the estimation of the true requirement under neutral circumstances, again making it difficult to establish a DRI (Institute of Medicine, 2011).

Statement of Purpose

The IOM committee has made recommendations on what the intake of vit. D should be for the public and specifically during pregnancy. This paper examined the current

recommendations for vit. D and how that compares to what pregnant women are taking and what new research is saying after 2011. It examined adequacy and deficiency of vit. D during pregnancy, sources of vit. D and optimum levels of vit. D.

Brief Review of Literature

In 2010 the IOM set the RDA for vit. D at 600 IU per day for pregnant women (Institute of Medicine, 2011). Studies have shown that vit. D deficiency is common during pregnancy, suggesting that a higher amount may be required during this time. Vitamin D deficiency during pregnancy has been associated with increased risk of preterm birth, preeclampsia, cesarean section delivery, gestational diabetes mellitus and risk for having small for gestational age infants (Finer, et al., 2012).

Several studies examined in this paper have concluded that vit. D supplementation during pregnancy will raise 25(OH)D levels and that adequate levels of vit (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011). D during pregnancy might reduce risk for preterm birth, preeclampsia and low birth weight. High concentrations of vitamin D are not found in many foods and prenatal supplements usually contain 400 IU. One of the main sources of vit. D include sunlight exposure which can be dependent on many things. Factors include skin color, amount of skin exposed, duration of exposure, use of sunscreen and latitude. It is thought that vit. D supplementation throughout pregnancy is needed to achieve adequate serum 25(OH)D levels to benefit maternal and fetal health. Some studies suggest that 4,000 IU per day should be taken by pregnant women so all women, regardless of race, attain optimal nutritional and hormonal vit. D levels throughout their pregnancies (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011).

Importance of Vitamin D during Pregnancy

During pregnancy, low vit. D status can be associated with increased adverse outcomes for the mother and infant. Vitamin D is important during pregnancy because the fetus relies on the mother as a source during development. Studies have shown that vit. D status among the mother correlates to the vit. D status of the infant (De-Regil LM, 2016). Vitamin D function during pregnancy can also have potential effects on certain systems including immune, pancreatic, musculoskeletal and cardiovascular function along with neural development (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011).

During pregnancy vit. D facilitates crucial transfer of calcium from the mother to child for proper skeletal development (Finer, et al., 2012). Finer et al. (2012) also suggested that maternal vit. D deficiency may cause increased risk of developing preeclampsia, cesarean section delivery, gestational diabetes and low birth weight for gestational age (Finer, et al., 2012). Neonatal vit. D levels are also dependent on the maternal vit. D status at delivery (Marshall, Mehta, & Petrova, 2013). vit. D status is proposed to influence brain development and neonatal immune function (Roth, et al., 2013). Finer et al. (2012) suggest conflicting results and highlight the need for further investigation and consideration of the complex relationship between vit. D status and ethnicity, complex dietary, lifestyle and social factors (Finer, et al., 2012). Other studies cite insufficient evidence to either support or refute the benefits of supplemental vit. D during pregnancy (Roth, et al., 2013).

What is Considered Adequate during Pregnancy?

The IOM considered the unique changes in physiology and nutrition needs that occur during pregnancy. When they considered the framework for the DRI they looked at the following factors: the need of the fetus during pregnancy, adaptation to increased nutrient demands such as

increased absorption and conservation of several nutrients, and the net loss of nutrients due to physiological mechanisms regardless of one's intake. The IOM also stated that, since during pregnancy there is an increase in absorption, conservation and net loss of nutrients that there might not be a basis for setting reference values for pregnant women that are different from values set for other women of the same age. The IOM concluded that the EAR for vit. D intake in pregnancy is 400 IU, the RDA is 600 IU and the UL is 4,000 IU (Institute of Medicine, 2011).

The Clinical practice guidelines from the Endocrine Society suggest that pregnant and lactating women require 600 IU of vit. D per day and recognize that at least 1,500-2,000 IU per day of vit. D might be needed to maintain serum 25(OH)D levels above 30 ng/ml. They suggest that maintenance tolerable upper limits of vit. D should not be exceeded without medical supervision, which is 4,000 IU of vit. D per day for everyone over the age of 8 years. They also recognize that higher levels up to 10,000 IU of vit. D per day for children and adults 19 years and older may be needed to correct vit. D deficiency. They suggest that all adults who are vit. D deficient be treated with 50,000 IU of vitamin D2 (vit. D2) or vitamin D3 (vit. D3) once a week for 8 weeks or the 6,000 IU equivalent of vit. D2 or vit. D3 daily for 8 weeks to achieve serum 25(OH)D levels above 30 ng/ml. This is then followed by a maintenance therapy dose of 1,500-2,000 IU per day (Holick, et al., 2011).

Research Findings Since 2011 about the Adequacy of Vitamin D during Pregnancy

Several studies since 2011 have been conducted on what intake of vit. D is considered adequate. Many of those studies concluded that the current recommendations of 600 IU per day of vit. D is not effective at achieving adequate circulating serum levels of 25(OH)D. One study by Hollis et al. (2011) found that supplementing with 4,000 IU of vit. D per day for pregnant women was safe and the most effective in achieving sufficiency among not only pregnant

women, but their offspring regardless of race (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011). Another study by Roth et al. (2013) concluded that doses upwards of 35,000 IU of vit. D per week may be used in research to help identify effects and safety of vit. D supplementation among pregnant women (Roth, et al., 2013). Mir et al. (2017) found that supplementation of 2,000 IU per day of vit. D or the monthly equivalent dose is more effective in achieving a higher vit. D level throughout pregnancy without an increase in the risk of toxicity to the mother or neonate (Mir, et al., 2017). Aghajafari et al. (2016) demonstrated that the current RDA of 600 IU of vit. D per day might not be enough to achieve a vit. D status above 30 ng/ml among some pregnant women who reside at higher latitudes. Researchers felt that recommendations for pregnant women needed to be re-evaluated (Aghajafari, et al., 2016). Hollick et al. (2011) suggested that pregnant and lactating women require 600 IU of vit. D per day and recognize that 1,500-2,000 IU per day of vit. D might be needed to maintain serum levels of 25(OH)D above 30 ng/ml (Holick, et al., 2011). They also suggested that dosing at upper limits (UL) of vit. D only be exceeded with medical supervision. There appears to be a disconnect between the IOM and ACOG's definitions of adequate intake of vit. D compared to what research suggests is adequate after 2011.

Objectives

1) Using evidenced based research, examined current recommendations of vit. D intake during pregnancy vs. recommendations after 2011 during pregnancy for vit. D intake.
2) Examined why adequate vit. D is important during pregnancy, screening for adequacy and deficiency of vit. D during pregnancy, sources of vit. D and optimum levels of vit. D.

Significance of Review

Women of childbearing age and healthcare professionals would benefit from knowing what the current recommendations are for vit. D intake to help prevent potential adverse effects deficiency might have on pregnancy. This review provides guidance on current recommendations for vit. D among pregnant women and what the most recent research suggests is adequate after 2011. It also examined adequacy and deficiency of vit. D during pregnancy, sources of vit. D and optimum levels of vit. D.

Definitions of Terms

Dietary Reference Intake (DRI): The general term for a set of reference values used to plan and assess nutrient intakes of healthy people. These values that vary by age and gender include the Recommended Dietary Allowance, Adequate Intake and Tolerable Upper Intake Level (National Institutes of Health, 2014).

Estimated Average Requirement (EAR): The estimated median requirement that is used for applications related to planning and assessing intakes for groups of people (Institute of Medicine, 2011).

Adequate Intake (AI): The adequate intake (AI) was established when evidence is insufficient to develop an RDA and is set at a level that is assumed to ensure nutritional adequacy (National Institutes of Health, 2014).

Recommended Dietary Allowance (RDA): The average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) of healthy people (National Institutes of Health, 2014).

Upper Intake Level (UL): The maximum daily intake unlikely to cause adverse health effects (National Institutes of Health, 2014).

25-hydroxyvitamin D (25(OH)D): Also known as calcidiol, made in the liver and converted to this from vit. D3 (cholecalciferol) and vit. D2 (ergocalciferol) (Lundqvist, Sandstrom, Stenlund, Johansson, & Hultdin, 2016).

International Unit (IU): It is a measurement based on biological activity or effect; 1 IU of vit. D is defined as the activity of 0.025 µg of cholecalciferol in bioassays with rats and chicks.

Conversions for vit. D3: 1 IU (International Unit) = 0.025 microgram (µg) cholecalciferol or ergocalciferol (Health, 2015).

Steps to Conducting Review

EBSCO host was searched due to being available through the NDSU library website. Search one used "vitamin D" and "pregnancy" as search terms that had full text, references available, and were peer reviewed between January 2011 and December 2017. Search one document types were article, language English, all publication types with pdf full text. Initially with search one there were 249 results. These were narrowed down to articles that were related to pregnancy only. Search two had the same search criteria, but used "vitamin D" and "maternal" instead of "pregnancy". There were 1675 results initially. Results were narrowed down to articles that related to pregnancy only. There were several articles also taken from the references of articles found in search one and two (Figure 1).

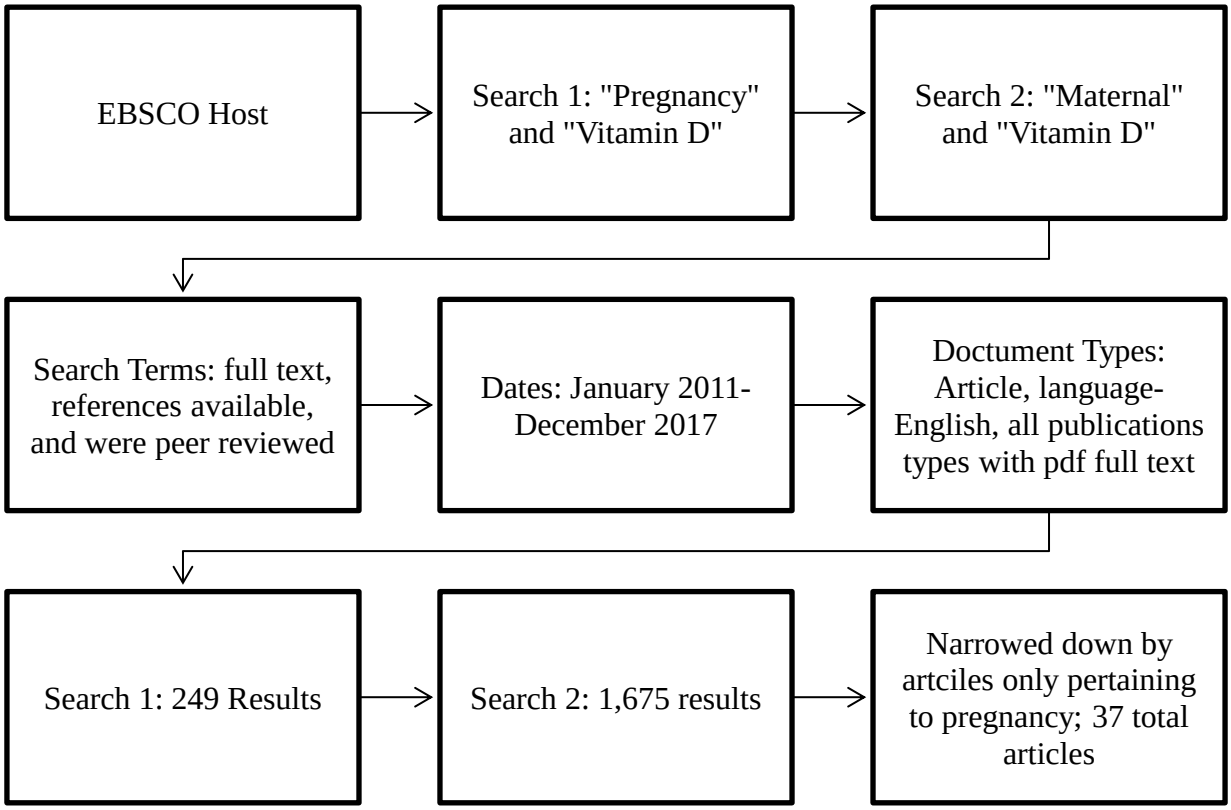

Figure 1. Steps to Conducting Review

Organization of Remaining Chapters

Chapter Two contains a review of the literature examining the following topics: Current recommendations on vit. D intake during pregnancy, sources of vit. D, sun exposure, vit. D storage, optimum serum levels of vit. D, vit. D deficiency and impact on pregnancy, and current intake among pregnant women of vit. D. A thorough literature search was conducted initially in 2014, and then repeated in 2015, 2016 and 2017. Chapter Three contains discussion and conclusions derived from the literature review. It also contains recommendations for future research and recommendations for pregnant women. Finally, all references were cited after chapter 3.

CHAPTER 2. REVIEW OF LITERATURE

Vitamin D

Vitamin D also known as the sunshine vitamin, was first recognized in the early twentieth century. It is identified now as a prohormone and can be synthesized by the human body through action of sunlight. Vitamin D is also known as calciferol. There are two major forms, vit. D2 and vit. D3. Vitamin D2 is a 28-carbon molecule that originates from ergosterol, known as ergocalciferol and a component of fungal cell membranes (Alshahrani & Aljohani, 2013). Vitamin D3 is a 27-carbon derived from cholesterol, known as cholecalciferol, and is synthesized in the skin of humans from 7-dehydrocholesterol. Vitamin D3 can also be consumed in the diet through animal-based foods. Both forms of vit. D are synthesized commercially and can be found in dietary supplements and fortified foods (Institute of Medicine, 2011).

Vitamin D2 and D3 differ only in their side chain structure, this difference does not affect metabolism (also known as activation) and both forms function as prohormones. Vitamin D in D2 or D3 form are considered biologically inactive until they undergo two reactions. These two reactions are enzymatic hydroxylation reactions. The first reaction takes place in the liver and is mediated by 25-hydroxylase, which then forms 25-hydroxyvitamin D (25(OH)D). The second reaction takes place in the kidney and is mediated by 1α-hydroxylase which converts 25(OH)D to the biologically active hormone named calcitriol. Calcitriol is also named 1, 25-dihydroxyvitamin D. 25(OH)D is the precursor of calcitriol and is also the major circulating form of vitamin D. Calcitriol circulates bound to a plasma carrier fibroblast protein called vitamin D binding protein (vit. DBP) (Institute of Medicine, 2011).

Renal synthesis of calcitriol is regulated tightly by two counteracting hormones, there is up-regulation through the parathyroid hormone (PTH) and down-regulation through fibroblast-

like growth factor-23 (FGF23). When there are low levels of serum phosphorus, calcitriol synthesis is stimulated. When there are high serum phosphorus levels calcitriol synthesis is inhibited. Once calcitriol is synthesized in the kidney, it binds to VDBP to be transported to target organs.

Vitamin D by itself is inactive, but the actions that vitamin D has on our bodies are because of the active metabolite, calcitriol. Calcitriol acts on the development and maintenance of bone health. Vitamin D Receptors (vit. DRs) are found throughout the body in tissues that are not involved with calcium and phosphate homeostasis. vit. DRs having a presence in body tissues implies that calcitriol may play a more general role on ligands other than calcitriol that can activate the vit. DR. Vitamin D-responsive elements (vit. DREs) are considered the hallmark of vit. D action. vit. DREs are present in many human genes that are involved in a wide range of classical and non-classical roles that include regulation of cell proliferation, cell differentiation, and apoptosis (Institute of Medicine, 2011). Throughout this paper serum 25(OH)D levels were addressed in ng/ml for consistency.

The IOM and most research on vit. D use serum concentrations of 25(OH)D as a measure of vit. D, as previously mentioned, because it reflects both intake from diet and cutaneous synthesis (Alshahrani & Aljohani, 2013), (Institute of Medicine, 2011). The IOM expresses vit. D quantities as International Units (IU). Vitamin D is also expressed as micrograms (μg) for which 1 μg is equal to 40 IU. The serum concentrations of 25(OH)D are expressed as nanomoles per liter (nmol/l) or another way to express this is nanograms per milliliter (ng/ml). If needed, the values that are expressed as nmol/l are divided by the conversation factor of 2.5 to obtain an equivalent measure in ng/ml (Institute of Medicine, 2011).

Vitamin D Recommendation by Institute of Medicine

When assessing vit. D requirements, the IOM considered what type of effects vit. D deficiency could lead to, e.g. alteration in bone health as evidenced by rickets in children and osteomalacia in adults. The main circulating form of vit. D is 25(OH)D and serum 25(OH)D concentrations are currently thought as the gold standard of measuring vit. D status. There is currently a lack of clarity on the impact several variables have on serum concentrations of 25(OH)D. The IOM recognized that serum 25(OH)D concentrations can reflect intake as it relates to bone health outcomes. Serum 25(OH)D concentrations have a dose-response relationship and is based under the impression that there is minimal sun exposure (Institute of Medicine, 2011).

The IOM committee made conclusions about serum 25(OH)D concentrations in relationship to the DRI development. The DRI was established based on conclusions that include, bone health specifically with calcium absorption, rickets, serum 25(OH)D level, fracture risk and osteomalacia (Institute of Medicine, 2011). A serum 25(OH)D concentration below 12 ng/ml is associated with increased risk of rickets, impaired fractional calcium absorption, decreased bone mineral content in children and adolescents, increased risk of osteomalacia; impaired fractional calcium absorption and increased risk of osteomalacia in young and middle-aged adults; and impaired fractional calcium absorption and fracture risk in older adults. The IOM committee concluded that serum 25(OH)D concentrations above 20 ng/ml did not have any additional benefit to any of the above indicators of bone health. Serum 25(OH)D concentration of 20 ng/ml is considered an adequate value to cover the needs of 97.5 percent of the population according to the IOM. The median requirement of serum 25(OH)D levels was estimated to be 16

ng/ml. A serum 25(OH)D value between 12 and 20 ng/ml for all age groups is an appropriate range of vit. D level per the IOM.

Specifications of vit. D among the DRI for adequacy were then established for each age group. The data gathered from the IOM committee were not sufficient to establish an EAR for infants under the age of 1 year so an AI was developed. There was not enough data to establish a DRI because the content of human milk does not shed light on the requirements of vit. D in infants, as breast milk is generally not a substantial source of vit. D. The AI for infants 0-6 months and 6-12 months was set at 400 IU of vit. D. The IOM committee found no data with clinical deficiency among infants who received daily intakes of 400 IU of vit. D. For children and adolescents 1-18 years of age, there was a focus for normal, healthy bone and is the basis for these DRI values. The EAR was set at 400 IU of vit. D and the RDA was set at 600 IU of vit. D (Institute of Medicine, 2011)(Table 1).

For adults 19-50 years of age, bone density maintenance was a focus when setting the EAR and RDA. Serum 25(OH)D concentrations regarding calcium absorption was the basis of establishing the DRI for vit. D in these adults. The IOM committee concluded that calcium absorption is maximal at serum 25(OH)D concentrations between 12-20 ng/ml and no increase of calcium absorption was noted above 20 ng/ml. Again, 400 IU daily was set as the EAR and an RDA of 600 IU daily was established for adults 19-50 years old (Institute of Medicine, 2011).

Dietary reference intake for adults 51-70 years old and those greater than the age of 70 was set on the ability to maintain bone density and decrease the level of bone loss. Fracture risk was also a central theme examined for establishing the DRI in this age group because those greater than 70 years of age are at a higher risk of mortality and morbidity associated with fractures. For adults 51-70 years old, other factors were considered in establishing the DRI that

affect daily requirements of vit. D. Impaired renal function, less efficient synthesis of vit. D in the skin, lower endogenous production of the active form of vit. D, increased PTH and age-related changes in body composition such as loss of muscle volume or muscle mass can affect daily requirements of vit. D. Institutionalization is also mentioned by the IOM committee that can affect the need for vit. D among this age group. An EAR of 400 IU daily and an RDA of 800 IU daily were set for this life stage group again, assuming minimal sun exposure (Table 2) (Institute of Medicine, 2011).

Vitamin D requirements during pregnancy and lactation were examined and based on AHRQ-Ottawa's findings and randomized control trials (Institute of Medicine, 2011). For both groups, an EAR of 400 IU and RDA of 600 IU daily were set (Institute of Medicine, 2011).

Table 2

Dietary Reference Intakes for Vitamin D for Individuals across the Lifespan

Life Stage Group	Estimated Average Requirement (IU/day)	Recommended Dietary Allowance (IU/day)	Upper Level Intake (IU/day)
Infants 0 to 6 months	*	*	1,000
Infants 6 to 12 months	*	*	1,500
1-3 years old	400	600	2,500
4-8 years old	400	600	3,000
9-13 years old	400	600	4,000
14-18 years old	400	600	4,000
19-30 years old	400	600	4,000
31-50 years old	400	600	4,000
51-70 years old	400	600	4,000
>70	400	800	4,000
14-18 years old, pregnant/lactating	400	600	4,000
19-50 years old, pregnant/lactating	400	600	4,000

*For infants, Adequate Intake (AI) is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age (Institute of Medicine, 2011)

Sources of Vitamin D

Sources of vit. D include sun exposure, food and dietary supplements. Few foods are natural sources of vit. D; such as fatty fish, fish liver oil and egg yolk. Other foods are fortified with vit. D, e.g. fluid milk in the United States. Other foods that are now being fortified with vit. D include ready-to-eat breakfast cereals, some milk substitutes, yogurts, cheeses, juices and

spreads in the U.S.; vit. D2 and vit. D3 are both used for fortification (Institute of Medicine, 2011).

Vitamin D is also synthesized in the skin from 7-dehydrocholesterol following sun exposure to ultraviolet B (UVB) radiation. The conversion of 7-dehydrocholesterol to the previtamin D3 depends on the amount of UVB radiation that reaches the dermis and availability of 7-dehydrocholesterol. Factors associated with the amount of vit. D that is synthesized from the skin depend on season of the year, skin pigmentation, latitude, use of sunscreen, clothing, adiposity, size (i.e. obesity) and frequency of dose and amount of skin that is exposed. Other factors include decline in vit. D synthesis with increasing age due to decrease in 7-dehydrocholesterol concentrations and to some extent because of alterations that occur in skin morphology. vit. D toxicity from the sun cannot occur, but toxicity from supplementing with vit. D is possible (Institute of Medicine, 2011). The first reports of hypervitaminosis D were around 1928-1932, consequences were hypercalcemia and soft tissue calcification that resulted in renal and cardiovascular damage (Institute of Medicine, 2011). Holick et al. (2011) stated that when an adult wearing a bathing suit is exposed to one minimal erythemal dose of UV radiation, which is when the skin has a slight pinkness to it 24 hours after sun exposure, this is equivalent to ingesting between 10,000 and 25,000 IU of vit. D in supplements. It is also noted that the vit. D that is produced in the skin potentially lasts twice as long in the blood compared to vit. D that is ingested (Holick, et al., 2011).

Vitamin D is a fat-soluble vitamin and is most efficiently absorbed with other dietary fats in the small intestine which also is dependent upon the presence of fat in the lumen. The optimal amount of fat needed for maximal absorption of vit. D has not yet been determined. If one does not have an adequate amount of bile or has pancreatic insufficiency this can reduce the

absorption of vit. D significantly (Institute of Medicine, 2011). There are very few foods that naturally contain vit. D2 or vit. D3 (Table 3).

Dawson-Hughes et al. (2015) tested the hypotheses that absorption of vit. D3 is greater when the supplement is taken alongside a meal that contains fat compared to one that was fat-free (Dawson-Hughes, et al., 2015). Also looking at if absorption is greater when the fat type in the meal is higher in monounsaturated-to-polyunsaturated fatty acid ratio (MUFA: PUFA). Researchers examined and open, three-group, single dose vit. D3 comparative absorption experiment. Participants consisted of 50 healthy older men and women randomly assigned to one of the three meal groups; fat-free meal, a meal with 30% of calories as fat with a low (1:4) and one with a high (4:1) MUFA: PUFA ratio (Dawson-Hughes, et al., 2015). Participants fasted for 12 hours and then all subjects took a single 50,000 IU dose of vit. D3 with their breakfast meal. Plasma vit. D3 levels were measured before, at 10, 12 and 14 hours after the dose. Plasma vit. D3 levels at mean peak (12-hours) was 32% greater in participants who consumed the fat-containing meal compared to the fat-free meal. The absorption did not differ significantly at any point in the high and low MUFA and PUFA groups (Dawson-Hughes, et al., 2015). Researchers concluded that when fat is present at a meal in which a vit. D3 supplement is taken significantly enhances absorption of the supplement. The amount of MUFA vs. PUFA contained in the meal does not influence absorption (Dawson-Hughes, et al., 2015).

Table 3

Natural Sources of Vitamin D2 and Vitamin D3

Source	Vitamin D content
Cod liver oil	400-1,000 IU/teaspoon vit. D3
Salmon, fresh wild caught	600-1,000 IU/3.5 oz vit. D3
Salmon, fresh farmed	100-250 IU/3.5 oz vit. D3, vit. D2
Salmon, canned	300-600 IU/3.5 oz vit. D3
Sardines, canned	300 IU/3.5 oz vit. D3
Mackerel, canned	250 IU/3.5 oz vit. D3
Tuna, canned	236 IU/3.5 oz vit. D3
Shiitake mushrooms, fresh	100 IU/3.5 oz vit. D2
Shiitake mushrooms, sun-dried	1,600 IU/3.5 oz vit. D2
Egg yolk	20 IU/yolk vit. D3 or D2
Sunlight/UVB radiation	20,000 IU equivalent to sun exposure to 1 minimal erythemal dose in a bathing suit. Exposing arms and legs to 0.5 minimal erythemal dose is equivalent to consuming 3,000 IU vit. D3.

(Holick, et al., 2011)

The United States and Canada fortify milk with vit. D along with some bread products, orange juices, cereals, yogurts and cheese. In Europe, most countries do not fortify milk with vit. D because of a law that forbids the fortification of foods with vit. D. Some European countries are fortifying cereals, breads and margarine with vit. D. Multivitamin supplements in the United States contain 400-1,000 IU of vit. D2 or vit. D3 and vit. D3 supplements contain anywhere from

400-50,000 IU of vit. D3. Pharmaceutical sources in the United States only contain vit. D2 as 50,000 IU capsules or as a liquid with 8,000 IU (Table 4) (Holick, et al., 2011).

Table 4

Fortified Foods, Pharmaceutical Sources and Supplemental Sources of Vitamin D2 and Vitamin D3

Source	Vitamin D Content
Fortified Foods	
Fortified milk	100 IU/8 oz, usually vit. D3
Fortified orange juice	100 IU/8 oz vit. D3
Infant formulas	100 IU/8 oz vit. D3
Fortified yogurts	100 IU/8 oz, usually vit. D3
Fortified butter	56 IU/3.5 oz, usually vit. D3
Fortified margarine	429 IU/3.5 oz, usually vit. D3
Fortified cheeses	100 IU/3 oz, usually vit. D3
Fortified breakfast cereals	100 IU/serving, usually vit. D3
Pharmaceutical sources in the United States	
vit. D2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vit. D2) liquid	8,000 IU/ml
Supplemental Sources	
Multivitamin	400, 500, 1,000 IU vit. D3 or vit. D2
vit. D3	400, 800, 1,000, 2,000, 5,000, 10,000 and 50,000 IU

(Holick, et al., 2011)

Sun Exposure and Vitamin D

Factors that the IOM considered in the estimation of DRI for vit. D include sun exposure and vit. D synthesis. Other aspects considered were public health recommendations that regard the need to limit sun exposure to avoid cancer risk. The IOM committee also assumed that entities who are going to use the DRI values for health policy or public health applications would adjust their considerations in relation to adequacy of the diet based on if the population of interest is minimally, moderately, or highly exposed to sunlight (Institute of Medicine, 2011).

Toxicity of vit. D cannot occur during prolonged periods of UV radiation exposure. There is a steady state reached in which 10-15% of cutaneous 7-dehydrocholesterol is converted to previtamin D3 (Tsiaras & Weinstock, 2011). It is suggested that this process of photoregulation ensures that toxic levels of vit. D3 are not synthesized under condition of excessive sun exposure (Tsiaras & Weinstock, 2011). When vit. D is synthesized cutaneously, it is then released from the plasma membrane and enters the systemic circulation bound to vit. DPB. Serum concentrations of vit. D3 peaks at 24-48 hours after UV radiation exposure. vit. D3 serum half-life ranges from 36-78 hours. Vitamin D3 can also be taken up by adipocytes and stored in subcutaneous or omental fat deposits for later use (Tsiaras & Weinstock, 2011). This distribution of vit. D3 into adipose tissue prolongs the total-body half-life to about two months (Tsiaras & Weinstock, 2011). Factors that affect cutaneous synthesis of vit. D include exposure to ultraviolet radiation. Processes that alter the amount of UVB radiation entering the skin can affect vit. D3 production. UVB radiation is the portion of electromagnetic spectrum between 280 nm and 320 nm. Optimum wavelengths for production of vit. D3 are between 295 nm and 300 nm with peak production at 297 nm (Tsiaras & Weinstock, 2011). The amount of UVB radiation that can reach the earth's surface is influenced by many factors. Those factors include the ozone,

substances UVB must travel through such as oxygen, nitrogen, aerosols, water vapor, particulate pollutants and cloud matter (Tsiaras & Weinstock, 2011). The time of year, time of day and latitude also affect UVB radiation. UBV radiation reaches a maximum at mid-day in the summer months, with latitudes below 35˚ North having sufficient UVB radiation for vit. D3 production all year long (Tsiaras & Weinstock, 2011). At higher latitudes vit. D3 cannot be produced in the winter months. At a latitude of 41.9˚ North, Rome, Italy has no cutaneous synthesis of vit. D3 from November through February. When going ten degrees further North at a latitude of 52.5˚ North Berlin, Germany, one cannot produce cutaneous synthesis of vit. D3 from October to April (Tsiaras & Weinstock, 2011). The latitude of Fargo, ND is 46.9˚ North (Longitude, 2016).

Sun protection is recommended for skin cancer prevention; hence, Linos et al. (2012) examined the relationship between different types of sun protective behaviors and serum 25(OH)D concentrations in the general US population (Linos, et al., 2012). This cross-sectional study collected data from 5,920 adults aged 18-60 years old. Individuals provided data as part of the 2003-2006 US National Health and Nutrition Examination Survey (NHANES). Sun protective behaviors were analyzed. The primary outcomes were serum 25(OH)D concentrations and vit. D deficiency. Vitamin D deficiency was defined as 25(OH)D concentrations <20 ng/ml. Staying in the shade and wearing long sleeves were significantly associated with lower 25(OH)D concentrations. The associations were most significant for whites compared to Hispanics or blacks. White participants who reported that they frequently stayed in the shade or wore long sleeves had double the odds of vit. D deficiency compared with those who rarely did so. Frequent sunscreen use and wearing a hat did not have an impact on 25(OH)D concentrations or vit. D deficiency (Linos, et al., 2012).

One randomized controlled trial examined UVB radiation and how it increases serum vit. D levels, expressed as 25-hydroxyvitamin D_3 (25(OH)D3) in a dose-response relationship (Bogh, Schmedes, Philipsen, Thieden, & Wulf, 2010). Researchers examined 172 fair-skinned persons. Participants were screened for 25(OH)D3 levels and then selected and randomized into one of eleven groups with five participants in each group. Each of the groups was exposed to one of four different UVB doses for 1, 5, 10 or 20 minutes. The study participants had four different UVB sessions with a 2-3-day interval between and 24% of their skin exposed. The skin pigmentation and 25(OH)D3 levels were measured before and after UVB exposure. The increase in 25(OH)D3 levels after exposure was positively correlated with the UVB dose but not to the dose rate (1-20 minutes). Researchers found that the increase in 25(OH)D3 levels after UVB exposure was achieved with very low UVB doses which was around 4 minutes at noon time in the summer (Bogh, Schmedes, Philipsen, Thieden, & Wulf, 2010).

The American Academy of Dermatology (AAD) points out in their position statement on vit. D that there is no scientifically validated safe threshold of UV exposure from the sun or indoor tanning devices that will allow for max vit. D synthesis without increasing skin cancer risk. The Academy further recommend the use of a comprehensive photo protective regimen that includes the regular use and proper use of broad-spectrum sunscreen. The AAD also summarizes the current IOM recommendations and DRI for vit. D, pointing out specifically that the RDA was derived based on minimal or no sun exposure. In conclusion, the AAD states that vit. D should be obtained from a healthy diet that includes foods naturally rich in vit. D, foods/beverages fortified with vit. D, and/or vit. D supplements and that vit. D should not be obtained from unprotected exposure to ultraviolet radiation (AAD, 2010).

Since cutaneous synthesis is an important source of vitamin D, another study by Farrar et al. (2013) examined the efficacy of a dose range of simulated summer sunlight exposures in raising vitamin D status among UK adults of South Asian ethnicity (Farrar, et al., 2013). This was a dose-response study among 60 healthy adults of South Asian ethnicity, 20-60 years old. Participants received 1 of 6 ultraviolet exposures that were equivalent to 15-90 minutes of unshaded noontime summer sunlight at 53.5 degrees north. The ultraviolet exposure was 3 times per week for 6 weeks while wearing casual clothes that revealed about 35% skin area. Serum 25(OH)D concentrations were measured weekly and dietary vitamin D intake was estimated. Most participants (n=51) at baseline were vit. D insufficient with serum 25(OH)D concentrations <20 ng/ml (Farrar, et al., 2013). All participants had a significant increase in 25(OH)D concentrations. This study gives insight to how sunlight exposure can usefully enhance vitamin D status to avoid deficiency. Optimal sun exposure was found to be equivalent to 45 minutes of unshaded noontime exposure 3 times weekly with 35% of skin surface area exposed among people of South Asian ethnicity to prevent vit. D deficiency and reach a vit. D status >10 ng/ml (Farrar, et al., 2013).

Casual exposure to sunlight is generally thought to provide enough sun exposure for vit. D requirements. Webb et al. (2010) examined if personal sunlight exposure levels could provide vit. D sufficiency, defined as serum 25(OH)D concentrations of ≥20 ng/ml and optimal levels, defined as serum 25(OH)D concentrations of >32 ng/ml among the U.K. public in a prospective cohort study (Webb, et al., 2010). Researchers measured circulating 25(OH)D concentrations monthly for 12 months in 109 white adults aged 20-60 years old in Greater Manchester. Intake of vitamin D through the diet and through personal ultraviolet radiation exposure were assessed over 1-2 weeks in each season of the year. Their primary analysis was to determine the post-

summer peak of 25(OH)D concentrations that are required to maintain vit. D sufficiency in wintertime. They found that intake through the diet remained low all year long through each season and personal ultraviolet radiation exposure levels were high in spring and summer, low in autumn and negligible in the winter season (Webb, et al., 2010). Their results also found that mean 25(OH)D concentrations were highest in September and lowest in February. Ultimately, they concluded that late summer 25(OH)D concentrations that approximate the optimal range are required to retain sufficiency throughout the U.K. winter. Much of the population failed to reach this post-summer level and became vitamin D insufficient during the winter. This indicates that the population requires more guidance in how to maintain vitamin D status more effectively and that public health policies on skin cancer need to take into consideration vitamin D requirements (Webb, et al., 2010).

Keumala et al. (2014) showed that vit. D deficiency can occur in women living in a tropical country who are likely exposed to more sun than women living in non-tropical countries (Keumala, Alrasyid, NurIndrawaty, & Zulkifli, 2014). This cross-sectional study was conducted on 156 healthy women during the dry season in North Sumatera. The study found that vit. D deficiency did exist among women in a tropical country and especially in those with less than 1 hour a day of sun ray exposure, having indoor occupations, inadequate intake of vit. D and those with low physical activity levels (Keumala, Alrasyid, NurIndrawaty, & Zulkifli, 2014). Also of interest only 5% of the studied population had sufficient vit. D levels defined as serum 25(OH)D concentrations 32-100 ng/ml. Ninety-five percent of participants were vit. D deficient, defined as serum 25(OH)D concentrations <20 ng/ml and insufficient, defined as serum 25(OH)D concentrations 20-32 ng/ml (Keumala, Alrasyid, NurIndrawaty, & Zulkifli, 2014).

Vitamin D Storage

In 1971 Rosenstreich et al. (1971) first showed that adipose tissue was the primary site of accumulation of vit. D. Vitamin D was radiolabeled in all body tissues by supplementing rats that were completely vit. D deficient with oral vit. D3 for 2 weeks. Rats were protected from sunlight by hanging cages in complete darkness. After supplementation, all vit. D was withheld and radioactivity and vit. D content in organs and tissues of rats was measured. Adipose tissue contained the greatest quantity of radioactivity throughout the 3-month experiment with the slowest rate of release. The researchers concluded that adipose tissue is the major storage site for vit. D3 in the absence of sunlight (Rosenstreich, Rich, & Volwiler, Deposition in and release of vitamin D3 from body fat: evidence for a storage site in the rat, 1971).

Wortsman et al's (2000) study showed that in obese subjects, vit. D was stored in adipose tissue and not released when it was needed (Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). This suggests that obese individuals likely require a larger amount of vit. D to achieve a serum 25(OH)D level that is similar to someone who is of normal weight. They concluded that obesity associated vit. D insufficiency is due to the decreased bioavailability of vit. D3 from cutaneous and dietary sources because of its deposition in body fat compartments (Wortsman, Matsuoka, Chen, Lu, & Holick, 2000).

Optimum Serum Levels of Vitamin D

Serum 25(OH)D is the major circulating form of vit. D. The half-life of vit. D is 2-3 weeks and is currently the best indicator to monitor vit. D status. Vitamin D adequacy, deficiency and insufficiency can be defined in different ways. This paper uses the Endocrine Society's recommendations to outline what serum 25(OH)D level is considered adequate, deficient or insufficient (Holick, et al., 2011). Vitamin D deficiency is defined as 25(OH)D

levels ≤20 ng/ml, vit. D insufficiency as 25(OH)D of 21-29 ng/ml. Adequacy is defined as serum 25(OH)D levels ≥30 ng/ml (Holick, et al., 2011). The IOM suggests that 20 ng/ml is an adequate vit. D level for the general population. This varies when considering different age groups; for example, children and adolescents 1-18 years of age, 16 and 20 ng/ml are considered adequate respectively.

Some studies suggested that for optimal calcium absorption vit. D concentrations need to be about 34 ng/ml, and for neuromuscular performance it is thought that vit. D concentrations need to be about 38 ng/ml (Alshahrani & Aljohani, 2013). Most experts collectively believe that 30 ng/ml is considered adequate (Alshahrani & Aljohani, 2013). Others still recommend a lower limit of 40 ng/ml due to the possibility of impaired calcium metabolism at this level. Clearly there is debate over what concentration is optimal for vit. D (Alshahrani & Aljohani 2013).

Vitamin D Deficiency and Impact on Pregnancy

One cause of vit. D deficiency among children and adults is inadequate sunlight exposure. The use of sunscreen with sun protection factor of 30 can reduce vit. D synthesis by the skin more than 95% and people who have naturally darker skin tone have an even more natural sun protection. Those with naturally darker skin tone might need three to five times longer exposure to sunlight to make the same amount of vit. D compared to a person with a white skin tone (Holick, et al., 2011). Another risk factor of vit. D deficiency is obesity. Ekwaru et al. (2014) found that vit. D supplementation might need to be 2-3 times higher for obese individuals (BMI <30 kg/m²) and 1.5 times higher for overweight individuals (BMI >25 kg/m² and ≤30 kg/m²) compared to normal weight individuals (BMI >18.5 kg/m² and ≤25 kg/m²) (Ekwaru, Zwicker, Holick, Giovannucci, & Veugelers, 2014). Individuals who are obese are at an increased risk for vit. D deficiency because body fat sequesters the fat-soluble vitamin

(Holick, et al., 2011). There are other medical diagnoses associated with vit. D deficiency such as patients with fat malabsorption syndromes like individuals with low bile amounts or pancreatic insufficiency with cystic fibrosis and patients that have had bariatric surgery who are unable to absorb the fat-soluble vitamins. Patients with nephrotic syndrome lose 25(OH)D through the urine due to 25(OH)D being bound to the vit. D-binding protein. Medications, such as anticonvulsants, glucocorticoids or AIDS treatments can cause an increased catabolism of 25(OH)D and 1,25-dihydroxyvitamin D_2 ($1,25(OH)_2D$) can be at an increased risk of vit. D deficiency (Holick, et al., 2011).

During the first and second trimesters in pregnancy, the fetus is working on developing its organ systems and laying down collagen matrix for its skeleton. In the third trimester, the fetus begins to calcify the skeleton which increases the maternal demand for calcium. This increased demand for calcium causes an increase in production of $1,25(OH)_2D$ by the mother's kidneys and placenta. Concentrations of circulating $1,25(OH)_2D$ increase gradually in the first and second trimesters because there is an increase in vit. D binding protein concentrations. Free levels of circulating $1,25(OH)_2D$ are responsible for enhancing intestinal calcium absorption and only increase in the third trimester. Pregnant women are at an increased risk for vit. D deficiency and consequences can range from preeclampsia to GDM (Holick, et al., 2011).

Deficiency of vit. D can result in abnormalities in calcium, phosphorus, and bone metabolism and more specifically vit. D deficiency can cause a decrease in the efficiency of intestinal calcium and phosphorus absorption of dietary calcium and phosphorus which results in an increase in PTH levels (Holick, et al., 2011). Griffiths et al. (2015) examined the effect of prenatal vit. D intake on healthcare utilization in the first three years of life (Griffiths, et al., 2015). Researchers proposed that observational studies have suggested that higher prenatal vit. D

intake might be associated with improved health outcomes in childhood, with mixed results. There were 180 women at 27 weeks gestation allocated to no vit. D, 800 IU ergocalciferol daily until delivery, or a single oral bolus of 200,000 IU cholecalciferol. Supplementation with vit. D increased maternal and cord blood 25(OH)D concentrations but the serum levels remained lower than current recommendations (Griffiths, et al., 2015). Researchers found no differences in total healthcare utilization costs between the control and daily or control and bolus groups. There were also no adverse effects of supplementation reported from vit. D supplementation. The vit. D doses provided from 27 weeks gestation to delivery failed to completely correct maternal vit. D deficiency suggesting a higher dose might be needed (Griffiths, et al., 2015).

Cadario et al. (2015) investigated 25(OH)D levels in maternal serum and neonatal blood spots among native and migrant populations living in Novara, North Italy which resides at 45˚N latitude (Cadario, et al., 2015). Researchers carried out a cross sectional study from April 1, 2012-March 30, 2013. Maternal blood samples after delivery and newborn blood spots were gathered and analyzed for 25(OH)D levels among 533 pairs. Country of origin, skin phototype, vit. D dietary intake and supplementation during pregnancy were recorded (Cadario, et al., 2015). Researchers found a link between neonatal and maternal 25(OH)D levels. Severely deficient 25(OH)D levels (<10 ng/ml) were found in 18% of Italian and 48.4% of migrant mothers, 38% of Italian and 76.2% of migrant newborns were also severely deficient. Serum 25(OH)D levels between 10-20 ng/ml which are deficient levels of vit. D were found in 43.6% of Italian and 41.3 % of migrant mothers and in 40.1% of Italian and 21.7% of migrant newborns (Cadario, et al., 2015). Italian mothers and their newborns had higher 25(OH)D levels than migrants and a linear decrease of 25(OH)D levels was found with increasing skin pigmentation. While vit. D supplementation resulted in higher 25(OH)D levels both in mothers and their

newborns (Cadario, et al., 2015). Researchers concluded that vit. D insufficiency in pregnancy and in newborns is frequent, especially among migrants. Researchers also urge there to be a prevention program so people identified as being at risk can be closely monitored and believe that vit. D supplementation should be thought out when considering a preventative health care policy (Cadario, et al., 2015).

Barati et al. (2016) aimed to evaluate the serum levels of vit. D among pregnant women at their first prenatal visit during their first trimester between February 2014 and February 2015 (Barati, Zarei, Moramezi, Saadati, & Masihi, 2016). Age, weight, BMI and gravid were recorded among 126 participants. Serum 25(OH)D levels and fasting blood sugar were checked, history of diabetes mellitus was also obtained. Blood levels of 25(OH)D ≤8 ng/ml were diagnosed as deficiency, 8-12 ng/ml as insufficiency and >12 ng/ml as normal. There were 85 participants found to have deficiency, 27 participants had insufficiency and 14 participants had normal vit. D levels. Among those who were overweight about 70.5% had low vit. D levels and in obese persons 64.3% had vit. D deficiency (Barati, Zarei, Moramezi, Saadati, & Masihi, 2016). All low weight persons suffered from vit. D deficiency. Despite an intense and sunny climate in almost all seasons in Pakistan, vit. D deficiency can be found in abundance. Researchers' recommendations are to measure levels of vit. D in the first trimester of pregnancy in all pregnant women (Barati, Zarei, Moramezi, Saadati, & Masihi, 2016).

De Laine et al. (2013) evaluated the vit. D status of pregnant women to assess the sensitivity of the current risk-based screening guidelines (De Laine, Matthews, & Grivell, 2013). Researchers conducted a prospective audit of vit. D levels of all women that presented for their first antenatal visit for three, four-week periods between 2009-2010 in South Australia (De Laine, Matthews, & Grivell, 2013). Levels of 25(OH)D3 were measured along with participants'

BMI, self-reported ethnicity and whether vit. D testing was indicated based on the hospital guidelines. Hospital guidelines included 'high-risk' groups who were veiled, dark-skinned and house-bound women, per the South Australian Perinatal Practice Guidelines (De Laine, Matthews, & Grivell, 2013). Participants consisted of 472 women, 67.4% were considered 'low-risk' for vit. D screening. Of these women, 46.2% and 78.6% of 'high-risk' women were vit. D deficient with levels <24 ng/ml. About 54.9% of women who were vit. D deficient were classified as 'low-risk' (De Laine, Matthews, & Grivell, 2013). Researchers found that risk-based screening criteria for vit. D deficiency failed to detect over half of vit. D deficient women at their institution. Researchers also agree that guidelines should include universal screening of vit. D for all pregnant women (De Laine, Matthews, & Grivell, 2013).

Xiao et al. (2015) aimed to evaluate the vit. D status of women in Eastern China during the second trimester of pregnancy (Xiao, et al., 2015). A cross-sectional observational study was conducted in a hospital in Wuxi, China (latitude 31.5˚N) where serum 25(OH)D concentrations were measured from 5,823 pregnant women from January 2011 to June 2012 (Xiao, et al., 2015). Vitamin D deficiency, 25(OH)D levels <12 ng/ml or inadequacy, 25(OH)D levels 12-20 ng/ml were identified in 40.7% and 38% of participants, respectively. There were only 0.9% of participants that had levels ≥32 ng/ml which is the level recommended as adequate by the Endocrine Society (Xiao, et al., 2015). Researchers found that younger women were more likely to be deficient in vit. D and there were significant differences in 25(OH)D levels according to season (Xiao, et al., 2015). In September 25(OH)D levels reached their peak values and fluctuated with average monthly air temperatures. Researchers ultimately found that there is a high prevalence of vit. D deficiency among pregnant Chinese women and that 25(OH)D levels varied according to season and air temperatures. Researchers also identify a large gap between

the levels of vit. D detected in pregnant Chinese women and the levels recommended by the Endocrine Society (Xiao, et al., 2015).

Pratumvinit et al. (2015) determined vit. D status among pregnant women and examined the factors that are associated with vit. D deficiency (Pratumvinit, et al., 2015). Researchers conducted a cross-sectional study of 147 pregnant Thai women between 18-45 years old in Bangkok, Thailand. Plasma levels of 25(OH)D, intact parathyroid hormone, calcium, albumin, phosphate and magnesium were obtained in pregnant women at delivery (Pratumvinit, et al., 2015). Hypovitaminosis D was defined as 25(OH)D levels <30 ng/ml which 75.5% of pregnant women had at delivery. Of the 75.5% of women with hypovitaminosis D 41.5% had vit. D insufficiency, defined as 25(OH)D of 20-30 ng/ml, and 34% were found to have vit. D deficiency, defined as 25(OH)D <20 ng/ml (Pratumvinit, et al., 2015). Researchers found that vit. D deficiency is common among pregnant Thai women. The prevalence of vit. D deficiency also increased in women who had a lower pre-pregnancy BMI and who's 25(OH)D levels were collected in the winter. Researchers suggested that vit. D supplementation may be needed as routine antenatal care (Pratumvinit, et al., 2015).

Lundqvist et al. (2016) studied longitudinally vit. D status during pregnancy and postpartum to identify the factors associated with vit. D status in pregnant women in Northern Sweden (Lundqvist, Sandstrom, Stenlund, Johansson, & Hultdin, 2016). There were 184 participants recruited between September 2006 and March 2009. Blood samples and dietary intake were estimated using a food frequency questionnaire and questions on intake of vitamin supplements at gestational weeks 12, 21 and 35 as well as 12 and 29 weeks postpartum (Lundqvist, Sandstrom, Stenlund, Johansson, & Hultdin, 2016). At least one third of participants had 25(OH)D levels <20 ng/ml on at least one sampling occasion. Plasma 25(OH)D levels

increased slightly over gestation period and peaked late in pregnancy and levels reverted to baseline after birth (Lundqvist, Sandstrom, Stenlund, Johansson, & Hultdin, 2016). Gestational and postpartum week, season, dietary intake of vit. D and vitamin supplementation were all significantly associated to plasma 25(OH)D levels. Season also influenced concentration patterns (Lundqvist, Sandstrom, Stenlund, Johansson, & Hultdin, 2016).

Rodriguez et al. (2016) assessed the prevalence and determinants of vit. D insufficiency and deficiency in pregnant women in Spain (Rodriguez, et al., 2016). Serum 25(OH)D3 levels were measured at the first trimester of gestation in 2,036 women from different geographical areas of Spain where the latitude ranges from 39-42˚ N. Insufficiency was defined as levels between 20-30 ng/ml and deficiency was defined as <20 ng/ml (Rodriguez, et al., 2016). Researchers found that 31% and 18% of women were vit. D insufficient and deficient, respectively. Independent determinants of 25(OH)D3 levels were season at collection, latitude, age, social class, tobacco smoking, physical activity and use of vit. D supplements (Rodriguez, et al., 2016). Summer season, Southern latitude, use of vit. D supplements, strong physical activity was associated with lower risk of vit. D insufficiency and deficiency. Researchers found a higher risk of vit. D deficiency in lower social class and those who smoke. Researchers concluded that vit. D insufficiency and deficiency are highly prevalent during pregnancy. Researchers also believed that recommendations and policies to detect and prevent low levels of vit. D during pregnancy should be developed (Rodriguez, et al., 2016).

Bergstrom et al. (2014) examined the prevalence of vit. D insufficiency in pregnant immigrant women by assessing 25(OH)D levels, parathyroid hormone and alkaline phosphatase as well as the correlation to musculoskeletal pain (Bergstrom, palmer, Persson, & Blanck, 2014). Participants consisted of 68 pregnant immigrant women and 51 native Swedish pregnant women

who served as controls. Levels of 25(OH)D, parathyroid hormone, alkaline phosphatase and musculoskeletal pain were analyzed in all women at 12 weeks and in the immigrant women at 6-12 months postpartum (Bergstrom, palmer, Persson, & Blanck, 2014). Among immigrant women, 77.9% had levels of 25(OH)D <10 ng/ml compared to only 3.9% in the control group. Among the immigrant women, 29.4% had 25(OH)D levels <4.8 ng/ml, none of the controls had a level this low. There was no correlation between 25(OH)D levels, parathyroid hormone or alkaline phosphatase and pain, but there was a significant negative correlation between changes in 25(OH)D and pain from 12 weeks gestation to postpartum (Bergstrom, palmer, Persson, & Blanck, 2014). Researchers found that low vit. D levels are prevalent among immigrant women who live in Sweden with an indication that pain might be associated with these low vit. D levels (Bergstrom, palmer, Persson, & Blanck, 2014).

Song et al. (2013) aimed to assess the vit. D status of pregnant women residing in Beijing (latitude of 39.9˚ N) in winter months (December 2010-February 2011) and evaluate the impact maternal factors have on serum 25(OH)D levels (Song, et al., 2013). Participants were 125 healthy pregnant women, data were collected regarding pre-pregnancy weight, educational status, use of multivitamins and other behavioral factors like duration of computer use, walking and sun exposure (Song, et al., 2013). Vitamin D deficiency, defined as 25(OH)D levels <20 ng/ml, was present among 96.8% of participants. Severe vit. D deficiency, defined as 25(OH)D levels <10 ng/ml, was present in 44.8% of participants (Song, et al., 2013). Levels of 25(OH)D were lower in women with shorter duration of sun exposure (≤0.5 hours per day) than those with longer duration of sun exposure (>0.5 hours per day). Even women who had sun exposure ≥1.5 hours per day had 25(OH)D concentrations of 12.8±3.6 ng/ml (Song, et al., 2013). Those participants who reported taking a multivitamin supplement had significantly higher 25(OH)D

levels when compared to non-users (Song, et al., 2013). Researchers concluded that pregnant women in Beijing are at very high risk of vit. D deficiency in winter and that duration of sun exposure and use of multivitamin were the most important determinants for vit. D status. Researchers also suggest that other measures may have to be taken for pregnant women to improve their vit. D status during the winter (Song, et al., 2013).

Luque-Fernandez et al. (2013) evaluated seasonal variation in 25(OH)D levels among pregnant women while focusing on patterns and determinants of variation (Luque-Fernandez, et al., 2013). Three cohort studies in the US included 2,583 non-Hispanic Black and White women who had prenatal 25(OH)D levels determined. Researchers observed a peak for 25(OH)D levels in the summer months and a low in the winter. The annual mean concentration of 25(OH)D levels for Black women were 19.8 ng/ml, for non-Hispanic White women were 33.0 ng/ml (Luque-Fernandez, et al., 2013). Researchers found that non-Hispanic Black women had lower average 25(OH)D levels throughout the year and a smaller seasonal variation than non-Hispanic White women. Researchers also confirmed that 25(OH)D levels had a seasonal variation over a calendar year, this information has the potential to enhance public health interventions targeted to improve maternal and perinatal outcomes (Luque-Fernandez, et al., 2013).

Zhao et al. (2012) looked at the prevalence and correlations of vit. D deficiency (25(OH)D levels<12 ng/ml) and inadequacy (25(OH)D levels <12-20 ng/ml) among US women of childbearing age (Zhao, Ford, Tsai, Li, & Croft, 2012). Researchers examined 1,814 female participants 20-44 years old in the 2003-2006 NHANES. Vitamin D deficiency and inadequacy were examined in participants. After age-adjustments, the prevalence of vit. D deficiency was 11.1% and 25.7% for vit. D inadequacy. Race/ethnicity other than for non-Hispanic white and obesity were associated with increased risks, where dietary supplement use, milk consumption

more than once per day and potential sunlight exposure during May-October were associated with decreased risks for vit. D deficiency and inadequacy (Zhao, Ford, Tsai, Li, & Croft, 2012). Current smokers, history of diabetes and cardiovascular disease were also associated with an increased risk for vit. D deficiency. Researchers concluded that among women of childbearing age, preconception intervention programs may focus on multiple risk factors for vit. D deficiency and inadequacy to help improve their vit. D nutrition (Zhao, Ford, Tsai, Li, & Croft, 2012).

Halicioglu et al. (2011) measured 25(OH)D3 levels among pregnant women in their last trimester and in their infants at delivery to determine the factors associated with maternal serum 25(OH)D3 concentrations (Halicioglu, et al., 2011). Data were collected between March to May 2008, 258 healthy pregnant women that were ≥37 weeks gestation were included in the study. Other factors examined were the number of pregnancies and births, nutritional status, vitamin and mineral support during gestation, educational status, clothing style and the economic level of the family (Halicioglu, et al., 2011). Mean 25(OH)D3 concentrations of mothers and their infants were 11.5±5.4 ng/ml and 11.5±6.8 ng/ml, respectively. Serum 25(OH)D levels were ≤20 ng/ml in 90.3% of mothers and within those with levels ≤20 ng/ml; 50.4% had levels ≤10 ng/ml (Halicioglu, et al., 2011). Serum 25(OH)D concentrations strongly correlated to those who had uncovered dressing style, sufficient consumption of dairy products and multivitamin use during pregnancy. Researchers concluded that despite sunny environments, vit. D deficiency and insufficiency are highly prevalent among mothers and their neonates, which is related to lifestyle and nutritional status of the mothers. Researchers suggested that a more proactive program be implemented for women and their babies regarding vit. D intake and supplementation (Halicioglu, et al., 2011).

Of the thirteen studies examined all have shown that vit. D deficiency is prevalent among pregnant women. Despite environments that are sunny, there continues to be vit. D deficiency among this population. It has been shown that increased vit. D supplement use and increased intake of vit. D rich foods decrease vit. D deficiency and inadequacy (Zhao, Ford, Tsai, Li, & Croft, 2012). One study finds that use of a multivitamin supplement is significantly associated with higher 25(OH)D levels which is beneficial to know since prevalence of deficiency is common (Song, et al., 2013). The color of one's skin and seasonal variation effects serum 25(OH)D levels and should be considered when screening pregnant women who might be deficient.

Obesity in Pregnancy and Vitamin D Deficiency

Obesity during pregnancy might be associated with reduced placental transfer of 25(OH)D to the fetus (Josefson, et al., 2016). Obese individuals are also known to have reduced bioavailability of 25(OH)D levels (Josefson, et al., 2016). Josefson et al. (2016) examined associations between maternal BMI and maternal and cord blood levels of 25(OH)D in full term neonates born to a single racial cohort who reside at similar latitudes (Josefson, et al., 2016). Secondary objects of the study were to examine the associations between maternal glucose tolerance with maternal levels of 25(OH)D and the relationship between cord blood 25(OH)D levels and neonatal size. Participants were a part of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. Participants met the following criteria: reside at latitudes between 41˚-43˚ North, maternal white race and gestational age between 39-41 weeks. There were 360 participants that had height, weight, and a 75-gram fasting oral glucose tolerance test at 28 weeks of gestation. Researchers found that maternal serum 25(OH)D levels were lower by 0.40 ng/ml for BMI higher by 1 kg/m² (Josefson, et al., 2016). Fasting plasma glucose, insulin sensitivity

and presence of GDM were not associated with maternal serum 25(OH)D levels when adjusting for maternal BMI. Cord blood 25(OH)D levels were also lower, by 0.26 ng/ml for maternal BMI higher by 1 kg/m². It has been suggested by the researchers that maternal 25(OH)D levels are associated with maternal BMI (Josefson, et al., 2016).

Another study by Lindsay et al. (2015) examining obese pregnant women aimed to assess maternal dietary and lifestyle habits (Lindsay, Heneghan, McNulty, Brennan, & McAuliffe, 2015). This was a prospective observational study that recruited 100 pregnant women with a BMI between 30.0-39.9 kg/m². Dietary intakes were assessed using a three-day food diary and a structured lifestyle questionnaire which assessed physical activity levels, smoking, alcohol habits and wellbeing (Lindsay, Heneghan, McNulty, Brennan, & McAuliffe, 2015). Researchers found that macronutrient intakes among obese pregnant women were not compliant to healthy eating guidelines with an inadequate intake of carbohydrate and excess intake of saturated fat. Intakes of calcium, iron, folate and vit. D were also poor from diet alone (Lindsay, Heneghan, McNulty, Brennan, & McAuliffe, 2015).

One study showed an inverse relationship between BMI and maternal serum 25(OH)D level showing that as BMI increases, serum 25(OH)D levels decrease (Josefson, et al., 2016). The other study examined found poor intakes of vitamin D among pregnant women who had BMIs between 30-39.9 kg/m² (Lindsay, Heneghan, McNulty, Brennan, & McAuliffe, 2015). With intake among pregnant women low in vit. D and an inverse relationship between BMI and serum 25(OH)D levels being prevalent, better prevention programs should be examined for this specific population or closer screening for women who are overweight (BMI ≥25.0-<30 kg/m²), obese (≥30.0-<40 kg/m²) or morbidly obese (BMI ≥40 kg/m²).

Preeclampsia in Pregnancy and Vitamin D Deficiency

Preeclampsia is a major obstetric complication which is defined as new onset of hypertension and proteinuria after 20 weeks of gestation (Alvarez-Fernandez, et al., 2015). Alvarez-Fernandez et al. (2015) examined the role of 25(OH)D levels and the soluble fms-like tyrosine kinase 1 to placental growth factor ratio in the development of early and late-onset preeclampsia and to evaluate the relationship between 25(OH)D (Alvarez-Fernandez, et al., 2015). The physiopathology of preeclampsia remains unclear but clinical signs and symptoms in preeclampsia seem to be the result of endothelial dysfunction. Among pregnant women, the placenta plays an important role by producing imbalanced concentrations of angiogenic (placental growth factor) and anti-angiogenic factors (soluble fms-like tyrosine kinase 1) which enters the maternal circulation causing such endothelial dysfunction (Alvarez-Fernandez, et al., 2015). Studies have shown high soluble fms-like tyrosine kinase 1 and low placental growth factors among women with preeclampsia. This was retrospective, full-blinded cohort study among 257 pregnant women. Women with preeclampsia showed lower 25(OH)D levels (mean level of 14 ng/ml) at clinical presentation than women who did not have preeclampsia (mean level of 16 ng/ml). Those women with serum 25(OH)D levels <20 ng/ml did experience an increased risk of developing late-onset preeclampsia but no association was found for early-onset preeclampsia (Alvarez-Fernandez, et al., 2015). Researchers concluded that low vit. D status among women with suspected late-onset preeclampsia increase the risk of development of the disease (Alvarez-Fernandez, et al., 2015).

Ringrose et al. (2011) examined the association between vit. D status and hypertension during late pregnancy (Ringrose, et al., 2011). Researchers conducted a case-control study during September-October 2008 and January-March 2009 among women who were near term.

Preeclampsia was defined as having two or more documented blood pressure readings above 140/90 mmHg at any time during pregnancy. There were 78 participants that met these criteria and 109 controls that had blood pressures below 140/90 mmHg during pregnancy. Serum 25(OH)D levels were measured in all participants (Ringrose, et al., 2011). During summer months, 13% of controls and 29% of the cases had 25(OH)D levels <20 ng/ml. During the winter months, these numbers rose to 44% and 49%, respectively with both cases and controls being more likely to have vit. D deficiency in the winter months (Ringrose, et al., 2011). Researchers noted a negative correlation between BMI and 25(OH)D levels and no difference in mean oral daily vit. D intake through diet and supplements. The controls gained less weight during pregnancy and there was a negative correlation between the highest blood pressure measured in pregnancy and 25(OH)D levels (Ringrose, et al., 2011). Researchers concluded that there is a high prevalence of vit. D deficiency in pregnant women in Saskatoon, Saskatchewan (latitude 52˚ North) and women with low circulating vit. D concentrations are more likely to have hypertension (Ringrose, et al., 2011).

Mirzakhani et al. (2016) assessed the effect of vit. D supplementation, 4,400 vs 400 IU per day, initiated between 10-18 weeks of gestation on the development of preeclampsia (Mirzakhani, et al., 2016). Effects of serum 25(OH)D levels on preeclampsia incidence at the beginning of the study and in the third trimester were studied (Mirzakhani, et al., 2016). Researchers also conducted a nested case-control study of 157 women to examine vit. D-associated gene expression profiles at 10-18 weeks among 47 participants who developed preeclampsia. Eight hundred and sixteen women were randomized and 67 (8.2%) developed preeclampsia. Among participants, there were no significant differences between the treatment and control groups in the incidence of preeclampsia (Mirzakhani, et al., 2016). Vitamin D levels

during the third trimester among those in the treatment group amounted to 39±15 ng/ml vs. 27±11 ng/ml in the placebo group. Preeclampsia happened in 33 women in the treatment group compared with 34 women in the placebo group. Vitamin D supplementation did increase 25(OH)D levels during the third trimester, however no reduction in the rate of preeclampsia was seen in the vit. D treatment group compared with that of the placebo group (Mirzakhani, et al., 2016). Women who had adequate vit. D levels (≥30 ng/ml) in both early and late pregnancy, regardless of treatment group, had significantly lower incidences of preeclampsia compared with those who had adequate levels at these same time points (Mirzakhani, et al., 2016).

Rezavand et al. (2016) compared serum levels of vit. D and interleukin-6 (inflammatory factors/cytokines) in healthy pregnant women and among those who had preeclampsia (Rezavand, et al., 2016). Researchers conducted a case-control study that was performed on 120 healthy pregnant women and 120 women who had preeclampsia. Serum 25(OH)D levels and interleukin-6 levels were obtained (Rezavand, et al., 2016). There was statistically no significant difference between mean vit. D levels in the patients and controls (37.64 ± 29.5 ng/ml and 40.06 ±33.20 ng/ml, respectively). Researchers did find higher serum levels of interleukin-6 among patients with preeclampsia compared to the control group. Researchers concluded that interleukin-6 levels can be considered risk factors for preeclampsia but more studies with a larger sample size are needed to evaluate the association between vit. D levels and risk of preeclampsia (Rezavand, et al., 2016).

Lechtermann et al. (2014) investigated the influence of season on maternal vit. D status and placental vit. D metabolism (Lechtermann, et al., 2014). Both 25(OH)D levels and $1,25(OH)_2D$ levels were measured during either the winter or summer months. Among 63 pregnant women at delivery, 43 were healthy pregnant women and 20 had preeclampsia

(Lechtermann, et al., 2014). Among patients with preeclampsia, 25(OH)D levels were lower but only varied significantly from the controls during summer months (18.21 ± 17.1 ng/ml vs 49.2 ± 29.2 ng/ml). Researchers found that maternal 25(OH)D levels produced significant results with an effect of season and preeclampsia. Researchers concluded that participants with preeclampsia had lower vit. D levels in response to seasonal changes (Lechtermann, et al., 2014).

Yu et al. (2013) aimed to determine if maternal serum levels of 25(OH)D during the first trimester of pregnancy were altered in cases that develop preeclampsia and if levels are related to biochemical and biophysical markers of impaired placental perfusion and function (Yu, Ertl, Skyfta, Akolekar, & Nicolaides, 2013). Total serum vit. D levels were obtained among 90 cases that developed preeclampsia, 30 required delivery before 34 weeks compared to 1,000 unaffected controls (Yu, Ertl, Skyfta, Akolekar, & Nicolaides, 2013). There were no significant differences in the median serum vit. D levels. Researchers concluded that among pregnant women who developed preeclampsia and those who did not, total serum 25(OH)D levels at 11-13 weeks gestation were no different (Yu, Ertl, Skyfta, Akolekar, & Nicolaides, 2013).

Of the six studies examined on preeclampsia, three had positive findings relating low serum 25(OH)D levels to hypertension or preeclampsia during pregnancy. Women who had lower 25(OH)D levels had increased chances of having hypertension in one study and another showed that higher levels of vit. D at the beginning pregnancy was associated with a lower risk of developing preeclampsia (Ringrose, et al., 2011) (Mirzakhani, et al., 2016). However, supplementation initiated early in pregnancy did not decrease the incidence of preeclampsia (Mirzakhani, et al., 2016). Season also played a role in 25(OH)D levels among participants with preeclampsia (Lechtermann, et al., 2014). These studies address the importance of having adequate serum 25(OH)D levels prior to pregnancy to help prevent preeclampsia. Two of the

studies examined did not find a correlation between serum 25(OH)D levels and preeclampsia and one of these studies citing need for a larger sample size to appropriate evaluate an association between vit. D levels and risk preeclampsia. One study had mixed results. It appears that further research with larger sample sizes are needed to adequately evaluate the association of vit. D levels and preeclampsia.

Gestational Diabetes Mellitus in Pregnancy and Vitamin D Deficiency

Deficiency of vit. D has been shown to be associated with GDM. Vitamin D induces insulin receptor expression through the vit. D receptor, enhancing insulin-dependent glucose transport (Liu, et al., 2017). Liu et al. (2017) studied the vit. D nutritional status of pregnant women with GDM in middle and late pregnancy and analyzed the different sources of vit. D intake (Liu, et al., 2017). Participants consisted of 98 pregnant women with GDM and subsequently divided into two groups, those who took a vit. D supplement and the control group. Levels of 25(OH)D and sources of vit. D intake and the frequency of food consumed rich in vit. D were explored (Liu, et al., 2017). The rate of vit. D deficiency (25(OH)D levels <20 ng/ml) was 20.4%. Eighty-four pregnant women took a vit. D supplement with a duration of 2 weeks to 31 weeks and an average daily dose of 517.5 ± 113.1 IU per day (Liu, et al., 2017). Participants who took a vit. D supplement had higher serum 25(OH)D levels than those who did not, the rates of deficiency were 17.9% and 35.7%, respectively. Researchers concluded that 20.4% of pregnant women with GDM in their middle to late pregnancy were deficient in vit. D though their levels were higher than the general population (Liu, et al., 2017).

O'Brien et al. (2017) aimed to determine if exposure to winter and low maternal 25(OH)D levels in early pregnancy were associated with maternal glucose metabolism (O'Brien, et al., 2017). Participants consisted of 334 pregnant women in Dublin, Ireland (latitude 51-55˚

North), serum 25(OH)D, fasting glucose, insulin and insulin resistance levels were measured at 12 weeks of gestation and at 28 weeks of gestation (O'Brien, et al., 2017). The season at the first antenatal visit was categorized as extended winter (November-April) or extended summer (May-October). Participants who attended their first antenatal visit during extended winter had lower 25(OH)D levels compared to those during extended summer (serum 25(OH)D levels 13.2 ng/ml vs. 17.6 ng/ml). When comparing those who attended their first antenatal visit during extended summer, extended winter was associated with increased insulin resistance levels in early pregnancy among 46.7% of participants and among 53.7% of late pregnancy participants (O'Brien, et al., 2017). During early pregnancy 25(OH)D levels <12 ng/ml and extended winter were independently associated with high fasting glucose levels in late pregnancy (O'Brien, et al., 2017). Researchers concluded that women who had their first antenatal visit during extended winter were more likely to have raised insulin resistance in early pregnancy which lasted to 28 weeks and was independent of 25(OH)D levels. It is implied that seasonal variation on insulin resistance may not be fully explained by differences in vit. D status, which requires further exploration (O'Brien, et al., 2017).

Dodds et al. (2016) explored associations between 25(OH)D levels and GDM and also determined if there was an interaction between smoking and 25(OH)D (Dodds, et al., 2016). Researchers conducted a nested case-control study in Halifax, Nova Scotia and Quebec City, Quebec. Women were recruited before 20 weeks of gestation and serum 25(OH)D levels were measured. There were 395 GDM cases and 1,925 controls. Controls were frequency matched to women with any of the study outcomes by site (Dodds, et al., 2016). Participants who smoked during pregnancy and had 25(OH)D levels <12 ng/ml compared to non-smokers with 25(OH)D levels ≥20 ng/ml (Dodds, et al., 2016). Researchers concluded that there is an inverse association

of vit. D status with GDM risk, especially among women who smoke during pregnancy (Dodds, et al., 2016). It is also acknowledged that more research is needed to confirm these findings (Dodds, et al., 2016).

Arnold et al. (2015) examined associations of vit. D status with GDM (Arnold, et al., 2015). Researchers conducted a nested case-cohort study with 135 GDM cases and 517 non-GDM controls, serum 25(OH)D and 25(OH)D3 levels were obtained at about 16 weeks (Arnold, et al., 2015). Of the GDM cases, there were lower mean total 25(OH)D (27.3 vs. 29.3 ng/ml) and 25(OH)D3 levels (23.9 vs. 26.7 ng/ml) compared with women who did not develop GDM (Arnold, et al., 2015). Researchers found that overall 25(OH)D3 levels, but not total 25(OH)D levels were significantly associated with GDM risk. Researchers also found that a 5 ng/ml increase in 25(OH)D3 levels was associated with a 14% decrease in GDM risk (Arnold, et al., 2015). Participants in the lowest quartile for 25(OH)D3 levels had a twofold higher risk of GDM compared to women in the highest quartile. Researchers concluded that vit. D status during pregnancy, especially 25(OH)D3, is inversely associated with GDM risk (Arnold, et al., 2015).

Researchers examining GDM found mixed results when linking serum 25(OH)D levels with GDM. Some studies found both positive and negative correlations. One study found prevalence of vit. D deficiency to GDM, but 25(OH)D levels of these women with GDM had higher 25(OH)D levels compared to the general population (Liu, et al., 2017). Season again played a role in insulin resistance but did not show a relationship to 25(OH)D levels in one study (O'Brien, et al., 2017). When evaluating the studies examined in this paper on GDM it appears that further research is needed to further evaluate a relationship between vit. D deficiency and GDM.

Preterm Birth in Pregnancy and Vitamin D Deficiency

One study showed that there is a reduced risk of preterm birth with vit. D supplementation (McDonnell, et al., 2017). McDonnell et al. (2017) aimed to determine if the reported inverse relationship between maternal 25(OH)D and preterm birth risk. Participants consisted of 1,064 pregnant patients between 18-45 years old. Women had 25(OH)D testing at their first prenatal visit with follow-up testing and free vit. D supplements of 5,000 IU per capsule were offered with a treatment goal ≥40 ng/ml. The overall preterm birth rate was 13% among women with a live, singleton birth and at least one 25(OH)D test during pregnancy (McDonnell, et al., 2017). Researchers found that women with 25(OH)D levels ≥40 ng/ml had a 62% lower risk of preterm birth compared to those with 25(OH)D levels <20 ng/ml (McDonnell, et al., 2017). Researchers also found that women with initial 25(OH)D levels <40 ng/ml, preterm birth rates were 60% lower for those with ≥40 ng/ml vs <40 ng/ml on a follow up test. Overall, researchers found that 25(OH)D concentrations ≥40 ng/ml were associated with substantial reduction in preterm birth risk (McDonnell, et al., 2017). McDonnell et al. (2017) found a positive correlation between serum 25(OH)D concentrations and preterm birth risk. Researchers state that vit. D testing and supplementation of pregnant women is a safe and affordable prevention tool that could help to substantially reduce the occurrence of preterm birth (McDonnell, et al., 2017).

Miscarriage in Pregnancy and Vitamin D Deficiency

Recurrent miscarriage happens in approximately 1-3% in couples of reproductive age, with several mechanisms described for the pathogenesis of recurrent miscarriage (Wang, et al., 2016). The 25-hydroxyvitamin D3-1α-hydroxylase (CYP27B1) is an integral part of the vit. D metabolic pathway. This enzyme catalyzes localized conversion of pro-hormone 25-

hydroxyvitamin D3 to the active form 1,25-dihydroxyvitamin D3 (Wang, et al., 2016). Wang et al. (2016) aimed to investigate the expression of CYP27B1 at the fetal-maternal interface in the first trimester of pregnancy and to determine if CYP27B1 was associated with recurrent miscarriage. Participants consisted of 20 women undergoing primary miscarriage and 20 women with recurrent miscarriage and another 20 women with normal pregnancy. Participants were examined for expressions of CYP27B1 mRNA and protein in villi and decidua (Wang, et al., 2016). Researchers found that women who had recurrent miscarriage had significantly lower expressions of CYP27B1 mRNA and protein in villous and decidual tissues compared to normal pregnant women. Concluding that women with recurrent miscarriage have lower level of CYP27B1 expression in chorionic villi and decidua compared with normal pregnant women which may suggest that reduced CYP27B1 expression may be associated with recurrent miscarriage (Wang, et al., 2016).

Depression and Anxiety in Pregnancy and Vitamin D Deficiency

Ten to fifteen percent of women worldwide experience postpartum depression, which is a significant public health problem (Nielsen, et al., 2013). Some epidemiological studies have shown evidence of an association between vit. D insufficiency and depression along with other mood disorders. The role for vit. D in various brain functions has been suggested (Nielsen, et al., 2013). Researchers hypothesized that a low vit. D status during pregnancy might increase the risk of postpartum depression and examined this in the research (Nielsen, et al., 2013). This was a case-control study among those in the Danish National Birth Cohort. Serum 25(OH)D3 levels were measured late in pregnancy among 605 women with postpartum depression and 875 controls (Nielsen, et al., 2013). Researchers found that results did not support an association between low maternal vit. D concentrations during pregnant and the risk of postpartum

depression. Researchers instead found an increased risk of postpartum depression among women with the highest vit. D concentrations >31.6 ng/ml compared to those with levels between 20-31.6 ng/ml (Nielsen, et al., 2013).

Huang et al. (2014) aimed to evaluate the associations between early pregnancy 25(OH)D levels and antepartum depression and anxiety symptoms (Huang, et al., 2014). Participants consisted of 498 pregnant women and researchers examined cross-sectional associations of early pregnancy serum 25(OH)D levels and depression and anxiety symptoms. Early pregnancy was a mean time of 15.4 weeks of gestation (Huang, et al., 2014). The mean 25(OH)D levels were 34.4 ng/ml among participants. There were about 12% of the study participants who had moderate anxiety and depression symptoms. Those with the lowest levels of vit. D, <28.9 ng/ml, had higher depression and anxiety scores than those in the highest quartile but associations were not statistically significant. Researchers did find an inverse association with 25(OH)D levels with depressive symptoms among those who reported no leisure-time physical activity (Huang, et al., 2014). Researchers concluded that there was modest evidence for inverse cross-sectional associations of early pregnant maternal vit. D levels with antepartum depression symptoms, which might be modified by physical activity (Huang, et al., 2014).

Of the two studies examining depression and anxiety as it relates to vit. D levels, one did not find a correlation and the other found a modest one. These studies show that an underlying mechanism is unclear for depression and anxiety during pregnancy as it relates to low vit. D levels. Further research is needed to investigate this potential relationship between depression, anxiety and vit. D levels.

Birthweight Outcomes in Pregnancy and Vitamin D Deficiency

Vitamin D status during pregnancy is linked to fetal grown and may impact infant growth (Eckhardt, Gernand, Roth, & Bodnar, 2015). Tian et al. (2016) measured maternal 25(OH)D levels in a nested case-control study (Tian, et al., 2016). Researchers tested the hypotheses that low maternal 25(OH)D levels during pregnancy are associated with decreased infant birthweight for gestational age, this association was modified by maternal race/ethnicity and infant sex. Participants consisted of 2,558 pregnant women from three cohorts. Maternal 25(OH)D levels were sampled at 4-29 weeks of gestation (Tian, et al., 2016). Among the non-Hispanic Black women, there was a positive association between 25(OH)D levels and infant birthweight for gestational age. Among the non-Hispanic White women, there was a positive association between 25(OH)D levels and infant birthweight for gestational age in male infants only (Tian, et al., 2016). Researchers concluded that serum 25(OH)D levels in early and mid-pregnancy were positively associated with infant birthweight for gestational age among non-Hispanic Black male and female infants and among non-Hispanic White male infants (Tian, et al., 2016).

Huang et al. (2013) assessed whether self-reported maternal birthweight was associated with risk of early pregnancy vit. D deficiency (defined as 25(OH)D levels ≤20 ng/ml) among 658 pregnant women (Huang, et al., 2013). Researchers adjusted for maternal characteristics and month of blood draw and noted a 100-gram higher maternal birthweight was associated with a 5.7% decreased risk of early pregnant 25(OH)D deficiency. Low birthweight (<2500 grams) women were 3.7 times as likely to have an early pregnancy 25(OH)D deficiency compared with normal-birthweight women (Huang, et al., 2013). Researchers concluded that further research on shared developmental mechanisms that determine birthweight and vit. D homeostasis may

possibly help identify targets and preventative measures for adverse pregnancy and birth outcomes (Huang, et al., 2013).

Berg et al. (2013) aimed to investigate the contribution of maternal 25(OH)D to the association of maternal education and small for gestational age birth weight (Berg, Eijsden, Vrijkotte, & Gemke, 2013). A second aim was to examine whether 25(OH)D levels differ by overweight, season and maternal smoking. Researchers examined 2,274 pregnant women of Dutch ethnicity. Results showed that low-educated women had lower 25(OH)D levels compared to highly educated women. Women in the lowest 25(OH)D quartile had a higher risk of small for gestational age offspring (Berg, Eijsden, Vrijkotte, & Gemke, 2013). Researchers concluded that 25(OH)D levels appear to be a modifiable contributor to the association between low maternal education and small for gestational age offspring particularly in overweight women and those who conceived in the winter months (Berg, Eijsden, Vrijkotte, & Gemke, 2013). Researchers also recommend that in those women it may be beneficial to increase the intake of vit. D either through dietary adjustments or through supplementation (Berg, Eijsden, Vrijkotte, & Gemke, 2013).

Eckhardt et al. (2015) examined the association between maternal vit. D status and infant anthropometry (Eckhardt, Gernand, Roth, & Bodnar, 2015). Participants consisted of 2,473 mother child pairs and maternal 25(OH)D levels were obtained at ≤26 weeks of gestation. Maternal vit. D status, infant z-scores for length, head circumference, weight and BMI were measured at birth, 4, 8 and 12 months in infants (Eckhardt, Gernand, Roth, & Bodnar, 2015). Almost one quarter of mothers had 25(OH)D levels <12 ng/ml and those women were more often overweight, obese and unmarried, African-American women and had lower socioeconomic index compared to women who had 25(OH)D levels ≥12 ng/ml. Infants whose mothers had

25(OH)D levels <12 ng/ml were smaller at birth weight in respects to all anthropometric measures compared to those infants who had mothers with 25(OH)D levels ≥12 ng/ml (Eckhardt, Gernand, Roth, & Bodnar, 2015). Researchers found that low maternal vit. D status was associated with deficits at birth infants' weight and BMI that were recouped during the first year of life. It was also found that associations with reduced measures of linear and skeletal growth were sustained from birth to 12 months (Eckhardt, Gernand, Roth, & Bodnar, 2015).

Of the four studies examined, all found a relationship to birthweight outcome and vit. D levels with just one having mixed results. Race, maternal education and being overweight plays a role in this relationship of vit. D levels to birthweight outcomes. More research is needed to better understand the relationship to birth weight outcome and vit. D levels. It is suggested that larger randomized controlled trials are needed to assess the effects vit. D supplementation have on fetal growth.

Multiple Outcomes Examined in Single Studies in Pregnancy and Vitamin D Deficiency

Flood-Nichols et al. (2015) analyzed the relationship between vit. D deficiency in the first trimester and subsequent clinical outcomes (Flood-Nichols, Tinnemore, Huang, Napolitano, & Ippolito, 2015). This study was a retrospective cohort. Participants consisted of 235 in their first trimester of women pregnant with their first child and with singleton gestations without significant medical problems (Flood-Nichols, Tinnemore, Huang, Napolitano, & Ippolito, 2015). Researchers found that 70% of participants were vit. D insufficient with serum concentrations <30 ng/ml. Adverse pregnancy outcomes comprised of preeclampsia, growth restriction, preterm delivery, gestational diabetes and spontaneous abortion (Flood-Nichols, Tinnemore, Huang, Napolitano, & Ippolito, 2015). Vitamin D deficiency was not associated with adverse pregnancy

outcomes in this study. Researchers did note a high percentage of young, reproductive-aged women with vit. D deficiency (Flood-Nichols, Tinnemore, Huang, Napolitano, & Ippolito, 2015).

Domaracki et al. (2016) examined concentrations of 25(OH)D levels in Polish women who had normal pregnancies and in pregnancies complicated by gestational hypertension, preeclampsia or gestational diabetes mellitus (Domaracki, et al., 2016). Researchers analyzed the associations between maternal serum 25(OH)D levels and the risk of gestational hypertension, preeclampsia and gestational diabetes mellitus among 207 pregnant women. Among participants, 171 women had pregnancy-related complications, the control group consisted of 36 women with normal pregnancies (Domaracki, et al., 2016). Participants with hypertension did not differ significantly from the controls in terms of serum 25(OH)D levels (18.2 vs 22.1 ng/ml). There was a highly significant difference found in serum 25(OH)D concentrations among women with preeclampsia and the controls (14.75 vs 22.1 ng/ml) (Domaracki, et al., 2016). Gestational diabetes mellitus was not associated with significant differences in 25(OH)D levels. Researchers found that 25(OH)D deficiency is common among pregnant Polish women and that low concentrations of 25(OH)D may play a role in the etiopathogenesis of preeclampsia. It is suggested that assessment of 25(OH)D levels during pregnancy may be important for the identification of women at increased risk of preeclampsia (Domaracki, et al., 2016).

Zhou et al. (2014) aimed to assess maternal 25(OH)D status and its association with pregnancy outcomes in a prospective observational study that was carried out in Guangzhou, China (latitude 23˚ North) (Zhou, et al., 2014). Participants consisted of 2,960 pregnant women and 100 healthy controls. Among participants, 18.9% had low 25(OH)D levels ≤20 ng/ml and 48.6% had medium levels 21-29 ng/ml (Zhou, et al., 2014). Serum 25(OH)D levels were the

highest in summer months and lowest in the winter months. Most maternal and infant outcomes were not associated with 25(OH)D levels but the prevalence of GDM and preterm delivery were noted in the high-level group with 25(OH)D levels ≥30 ng/ml than with the low and medium level groups (Zhou, et al., 2014).

Moller et al. (2012) studied the effects of pre-conception 25(OH)D levels on changes for pregnancy as well as the effects during pregnancy on the risk of miscarriage, birth weight and length, Apgar score and head circumferences (Moller, Streym, Heickendorff, Mosekilde, & Rejnmark, 2012). Participants consisted of 153 healthy Caucasian women with pregnancy plans and 75 non-pregnant, age-matched women were followed as controls. Baseline 25(OH)D levels were 23.6 ng/ml, 31% had levels < 23.6 ng/ml and 12% had levels above 32 ng/ml (Moller, Streym, Heickendorff, Mosekilde, & Rejnmark, 2012). Serum 25(OH)D levels were not associated with the changes of conceiving or overall risk of miscarriage; however, those women with a miscarriage in their second trimester had lower 25(OH)D levels compared to those without miscarriage. Levels of 25(OH)D before or during pregnancy were not associated with gestational length or infant parameters. Researchers concluded that 25(OH)D levels prior to conception did not affect fertility or pregnancy outcomes, but low 25(OH)D levels may be associated with an increased risk of late miscarriage (Moller, Streym, Heickendorff, Mosekilde, & Rejnmark, 2012).

When examining studies that had several outcomes there were mixed correlations between vit. D and outcomes. Some studies found no correlation to adverse pregnancy outcomes and 25(OH)D levels. Some studies found a correlation between one adverse pregnancy outcome but not all the adverse outcomes. Correlations were found to exist between 25(OH)D levels and preeclampsia, GDM, preterm delivery, miscarriage in the second trimester.

Current Intake of Vitamin D by Pregnant Women

One randomized controlled trial among women with a single pregnancy were examined at 12-16 weeks of gestation. Women were supplemented with 400, 2,000 or 4,000 IU of vit. D3 daily until they delivered (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011). Maternal and neonatal circulating 25(OH)D levels were examined at delivery. There were 350 women that continued in the study until delivery. The mean 25(OH)D level at delivery and one month before delivery was significantly different. Those who took 4,000 IU had the greatest percent in their group who achieved sufficiency. There were no differences between groups on safety measures and there were no adverse events that were attributed to vit. D supplementation or circulating 25(OH)D levels (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011). Supplementing with 4,000 IU of vit. D for pregnant women was safe and the most effective, compared to 400 IU and 2,000 IU in achieving sufficiency among women and their neonates regardless of race. The researchers concluded that the current estimated average requirement was not effective at achieving adequate circulating 25(OH)D, especially among African Americans (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011).

A collaborative, multi-center, birth cohort study was conducted in nine European countries whom obtained standardized baseline information from 12,049 participants (Oliver, et al., 2014). Pregnancy recommendations were also obtained from all countries. The standardized baseline questionnaire data included details of food intake, nutritional supplement use, exposure to cigarette smoke and socio-demographic data during pregnancy (Oliver, et al., 2014). Vitamin D supplementation among participants in the entire cohort was very poor; 0.3%-5.1%. Only four out of nine countries in this cohort made specific recommendations for pregnant women to take

vit. D. Researchers thought this was due to the assumption that sunshine exposure was adequate among participants (Oliver, et al., 2014).

Morisset et al. (2016) examined iron, vit. D and calcium intakes from diet and supplements in relation to maternal characteristics (Morisset, et al., 2016). Data were collected in 1,186 pregnant women from the Maternal-Infant Research on Environmental Chemicals Study, which was a cohort study among pregnant women recruited from 10 Canadian sites between 2008-2011. Researchers administered a food frequency questionnaire to obtain rankings of iron, calcium and vit. D intake at 16-21 weeks of gestation. Supplement intake was obtained from a separate questionnaire at 6-13 weeks of gestation (Morisset, et al., 2016). Intake of supplements was an important contributor to total iron intake and total vit. D intake while the contrary was observed for calcium intake. Being born outside of Canada was associated significantly with lower total intakes of iron, vit. D and calcium. Supplement use was a consistently positive indicator when maternal age was over 30 years and with women who held university degrees. Researchers found that supplement intake was a major contributor to total iron and vit. D intakes and higher education level and being over 30 years old (Morisset, et al., 2016).

Roth et al. (2013) conducted a double-blind placebo-controlled randomized trial to evaluate effectiveness of a high-dose vit. D supplementation in the prenatal third trimester and outcomes it had on the maternal and neonatal (cord blood) serum 25(OH)D (Roth D. E., et al., 2013). Participants consisted of women 18-<35 years old, at 26-<29 weeks of gestation. There were 130 women who participated. Women were randomized 1:1 to one of two intervention groups. The first intervention group was given a placebo (n=63) and the second intervention group was given 35,000 IU of vit. D3 (vit. D3) (n=67) until delivery (Roth D. E., et al., 2013). Baseline levels of serum 25(OH)D concentrations were similar among the vit. D and placebo

groups. At delivery, serum 25(OH)D levels were significantly higher in the vit. D group versus the placebo group. One hundred percent of the supplemented mothers and 95% of the neonates attained a serum 25(OH)D level greater than 20 ng/ml versus 21% of mothers and 19% of neonates in the placebo group (Roth D. E., et al., 2013). There were no supplement-related adverse events or major adverse pregnancy outcomes among both study groups. It is concluded from this study that doses up to 35,000 IU per week of vit. D3 may be cautiously used in research to help establish clinical effects and safety of vit. D3 supplementation among pregnant women (Roth, et al., 2013).

An open-label, parallel group, prospective randomized and controlled trial was conducted to assess the efficacy and safety of various doses of vit. D during pregnancy (Mir, et al., 2017). There were 87 women who completed the study. Subjects were assigned to four treatment groups. Women were enrolled from their first trimester to the start of the second trimester depending on when the pregnancy was confirmed. Group 1 took 1,000 IU of vit. D daily, group 2 took 30,000 IU of vit. D monthly, group 3 took 2,000 IU of vit. D daily and group 4 took 60,000 IU bolus of vit. D monthly. Post supplementation levels of 25(OH)D were higher in the 2,000 IU vit. D per day (group 3) and 60,000 IU vit. D per month (group 4) group (called group 2K) than the 1,000 IU vit. D per day (group 1) and 30,000 IU vit. D per month (group 3) group (called group 1K) (Mir, et al., 2017). Serum 25(OH)D in group 2K were 42.9±12.8 ng/ml compared to 37.0 +/-10.6 ng/ml in group 1K; p value was 0.023. The results also showed that group 4 (60,000 IU of vit. D per month) had significantly higher serum 25(OH)D levels than subjects in group 2 (30,000 IU of vit. D per month). Supplementation with 2,000 IU of vit. D per day or 60,0000 IU of vit. D per month was effective and safe in achieving vit. D sufficiency among pregnant women. In this study, vit. D sufficiency is defined as serum 25(OH)D levels of 30 ng/ml or

more. This study specifically demonstrates that daily or monthly doses of vit. D are equally effective in correcting vit. D levels at term. This study concludes that starting at 16 weeks of gestation, vit. D supplementation of 2,000 IU per day or the monthly equivalent dose is more effective in achieving a higher vit. D level throughout pregnancy without an increase in the risk of toxicity to the mother or neonate (Mir, et al., 2017).

Aghajafari et al. (2016) conducted a study to determine if pregnant women consumed the recommended vit. D through diet alone or through diet and supplementation and whether they achieved the current reference range of vit. D status when their reported dietary intake met current recommendations (Aghajafari, et al., 2016). Blood samples were collected in the second trimester from 537 women. They found a significant relationship between maternal reported dietary vit. D intake, through diet and supplements, and 25(OH)D and 3-epi-25-hydroxycholecalciferol levels. Women who had serum 25(OH)D concentrations <30 ng/ml reported consuming less vit. D through diet and supplements compared to those with serum levels ≥30 ng/ml (Aghajafari, et al., 2016). They also found that 44% of pregnant women with higher socioeconomic status reported vit. D intake through diet and supplements did not meet the DRI recommendations of 600 IU. Twenty percent of pregnant women had serum 25(OH)D levels <30 ng/ml despite over half of these women reporting intakes more than 600 IU/day of vit. D through diet and supplements. Fifty percent of the women who participated in this study were classified as vit. D insufficient, defined as vit. D level <30 ng/ml. Aghajafari et al. (2016) demonstrated that the current RDA of 600 IU of vit. D per day may not be enough to achieve vit. D status above 30 ng/ml in some pregnant women who reside at higher latitudes, and recommendations for pregnant women need to be re-evaluated (Aghajafari, et al., 2016).

Holick et al. (2011) created guidelines for clinicians for the evaluation, treatment and prevention of vit. D deficiency, which emphasized care of patients who are at risk for deficiency (Holick, et al., 2011). The task force which was reviewed by the Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee and cosponsoring associations acknowledged that vit. D deficiency is very common in all age groups and that few foods contain vit. D. Specific recommendations for pregnant and lactating women were evaluated and they suggest that this population requires 600 IU of vit. D per day and recognize that 1,500-2,000 IU per day of vit. D might be needed to maintain serum levels of 25(OH)D above 30 ng/ml (Holick, et al., 2011). The committee also suggested that maintenance of tolerable upper limits (UL) of vit. D only be exceeded with medical supervision. This amount is 4,000 IU of vit. D for everyone over 8 years old and potential for 10,000 IU per day of vit. D for children and adults 19 years and older to correct vit. D deficiency. The committee also suggested that adults who are vit. D deficient be treated with 50,000 IU of vit. D2 or vit. D3 once a week for 8 weeks or using the equivalent of 6,000 IU of vit. D2 or vit. D3 daily for 8 weeks to achieve serum 25(OH)D levels above 30 ng/ml and then followed by a maintenance dose of 1,500-2,000 IU per day of vit. D (Holick, et al., 2011).

McGowan et al. (2011) examined food groups that contribute to vit. D intake among pregnant women (McGowan, Byrne, Walsh, & McAuliffe, 2011). Researchers aimed to determine dietary intakes of vit. D throughout pregnant among 64 women and to determine the main food groups that contribute to vit. D intake. Dietary intake of vit. D ranged from 76-84 IU per day during pregnancy, with 80% below the current recommendations. The main food groups contributing to vit. D intake were meat, egg and breakfast cereals (McGowan, Byrne, Walsh, & McAuliffe, 2011). Researchers pointed out that oily fish is the best dietary source of vit. D

supplementation and this was consumed by less than 25% of women. Researchers point out that there needs to be more education among pregnant women and they also question the role of vit. D supplementation and highlight the contribution of other food groups that are more frequently consumed (McGowan, Byrne, Walsh, & McAuliffe, 2011).

There continues to be controversy over what constitutes vit. D adequacy and how much vit. D is needed to replete deficiency or maintain adequacy. Most studies to date do not show consistency with what the IOM recommends for vit. D and the DRI, especially during pregnancy. More research continues to be done on vit. D levels during pregnancy and there continue to be more studies on vit. D supplementation during pregnancy and what is considered safe dosages.

CHAPTER 3. DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

Vitamin D deficiency has substantial implications for human health throughout life and specifically during pregnancy. The IOM committee concluded that only skeletal health provided the one contributing outcome for establishing the DRI for calcium and vit. D (Institute of Medicine, 2011). Recent research after 2011 has shown that several outcomes related to pregnancy might also be a contributing factor for reevaluating the DRI for vit. D. Vitamin D during pregnancy is crucial for transfer of calcium from the mother to child for proper skeletal development, but it has also been suggested that maternal vit. D deficiency can cause a myriad of other issues during pregnancy. This review summarized the current recommendations for vit. D and how that compares to what pregnant women are taking and what new research is saying after 2011. It also examined adequacy and deficiency of vit. D during pregnancy, sources of vit. D and optimum levels of vit. D. Women of childbearing age and other healthcare professionals will benefit from knowing what the current recommendations are for vit. D intake to help prevent potential adverse effects deficiency might have on pregnancy. Due to numerous variables having effects on serum concentrations of 25(OH)D, it is difficult to narrow down what amounts of vit. D should be recommended during pregnancy and at times how they should be recommended. Since one of the main sources of vit. D is sun exposure, yet the recommendations are to limit sun exposure to avoid cancer risk, makes it difficult to recommend any certain way to obtain vit. D, through supplements, foods or sun exposure.

Thirteen studies that examined the prevalence of vit. D among pregnant women showed that vit. D is common. Despite environments that are sunny, there continues to be vit. D deficiency among pregnant women. It has been shown that increased vit. D supplement use and increased intake of vit. D rich foods decrease vit. D deficiency and inadequacy (Zhao, Ford, Tsai,

Li, & Croft, 2012). With one study stating that taking a multivitamin supplement was significantly associated with higher 25(OH)D levels (Song, et al., 2013). Skin color also played a role in vit. D levels among pregnant women and seasonal variation (Luque-Fernandez, et al., 2013) (Lundqvist, Sandstrom, Stenlund, Johansson, & Hultdin, 2016).

When examining vit. D deficiency and the impact it has on pregnancy there are mixed results and if there is relevance to serum 25(OH)D levels. Of the studies examined 11 showed correlation between serum 25(OH)D levels and adverse outcomes of pregnancy, 6 showed no correlation and 6 showed mixed results.

Limitations of this review include only using EBSCO host as a search engine through the online NDSU library. Another limitation is that only one person conducted the review process. Eligibility of research for inclusion and data extraction was assessed by just one person along with subjective judgements of that one person, whereas two persons going through eligibility of research might have been better. Choosing only the English language is another limitation since many research articles are also in other languages.

After examining research after 2011 when the DRIs were put out, it is unclear if bone health is the only basis for DRI development. It appears that more research is needed prior to the IOM conducting another evaluation on the DRI for calcium and vit. D. There continues to be a gap in high quality, larger randomized trials to evaluate the role of vit. D supplementation in pregnancy. Future research should continue to examine if an increase of serum 25(OH)D levels is associated with improved maternal and infant outcomes in populations with different skin pigmentation, sunscreen habits, BMI, GDM, preeclampsia and those living at different latitudes. Furthermore, there needs to be more information on the most effective and optimal safe dosage regimen of vit. D during pregnancy and to identify the safest repletion dose regimen for those

who are identified as deficient during pregnancy. At this time, it is not recommended that vit. D supplementation be given as routine antenatal care to all women to improve adverse pregnancy outcomes. Until further research is conducted health care professionals and RDNs should continue to advise pregnant women to consume a general healthful diet, a prenatal multivitamin that contains vit. D and to obtain vit. D through safe sun exposure if they are able.

Looking at current recommendations for vit. D and how it compares to more recent research. Numerous studies conducted after 2011 concluded that the current recommendations of 600 IU per day of vit. D is not effective at achieving adequate circulating serum levels of 25(OH)D. Research has shown a variety of dosing regimens safe and effective for pregnant women in helping to achieve sufficient 25(OH)D levels. Supplementation amounts varied in the research examined in this paper and research has demonstrated that the current RDA of 600 IU of vit. D per day might not be enough to achieve a vit. D status above 30 ng/ml among some pregnant women. Researchers felt that recommendations for pregnant women needed to be re-evaluated. It appears that intakes of ~2,000 IU per day is likely safe to consume during pregnancy. Studies show that there is a disconnect between the IOM and ACOG's definitions of adequate intake of vit. D compared to what research suggests is adequate after 2011.

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APPENDIX. SUMMARY OF ARTICLES, VITAMIN D DEFICIENCY AND IMPACT ON PREGNANCY AND CURRENT INTAKE OF VITAMIN D BY PREGNANT WOMEN

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Aghajafari et al. (2016)	537 pregnant women, March 2009-July 2012	Secondary analysis of a prospective cohort study	Determine if pregnant women consumed the recommended vit. D through diet alone or through diet and supplements and if they achieved the current reference range vit. D status when their reported dietary intake met the current recommendations.	The current RDA of 600 IU per day may not be adequate to achieve vit. D status >30 ng/ml in some pregnant women who are residing at higher latitudes and the current vit. D recommendations may need to be re-evaluated.
Alvarez-Fernandez et al. (2015)	257 pregnant women with suspicion of preeclampsia in Oviedo, Spain, January 2010-March 2013	Retrospective, full-blinded cohort	Assess the role of 25(OH)D concentrations and the soluble fms-like tyrosine kinase 1 to placental growth factor ratio in the development of early and late onset preeclampsia and to evaluate the relationship between 25(OH)D and biomarkers.	Low vit. D status in women with suspected late-onset preeclampsia increases the risk of imminent development of the disease.
Arnold et al. (2015)	135 pregnant women with GDM and 517 without GDM	Nested case-cohort study	Examined associations of vit. D status with GDM.	Early pregnancy vit. D levels, particularly 25(OH)D3 is inversely associated with GDM risk.
Barati et al. (2016)	126 pregnant Pakistanis women, February 2014-February 2015	Prospective cohort	Evaluate the serum levels of vit. D among pregnant women in their first prenatal visit.	Despite an intense and sunny climate in almost all seasons in Pakistan, vit. D deficiency can be found in abundance.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Berg et al. (2013)	2,274 pregnant women of Dutch ethnicity	Population-based cohort study	Investigate the contribution of maternal 25(OH)D vit. D to the association of maternal education and small for gestational age birth weight and to also examine whether the contribution of 25(OH)D differs by overweight, season and maternal smoking.	25(OH)D appears to be a modifiable contributor to the association between low maternal education and small for gestational age offspring, in overweight women and women who conceived in the winter.
Bergstrom et al. (2014)	68 pregnant immigrant women and 51 native Swedish women, 2006-2010	Population-based cohort study	Determine the prevalence of vit. D insufficiency in pregnant immigrant women assessed by the levels of 25(OH)D, parathyroid hormone and alkaline phosphatase and correlation to musculoskeletal pain.	Hypovitaminosis D is prevalent in immigrant women living in Sweden, there is a negative correlation between changes in 25(OH)D and pain from gestational week 12-postpartum.
Cadario et al. (2015)	533 Maternal and neonatal pairs, April 1, 2012-March 30, 2013	Cross sectional	Investigate 25(OH)D levels in maternal serum and neonatal blood spots among native and migrant populations living in Novara, Italy.	vit. D insufficiency in pregnancy and in newborns is frequent, especially among migrants.
DeLaine et al. (2013)	472 Pregnant women, three, four-week periods 2009-2010	Prospective audit	Evaluate the vit. D status of pregnant women at their institution and assess the sensitivity of the current risk-based screen guideline.	Risk-based screening criteria for vit. D deficiency in pregnancy fails to detect over half of vit. D deficient women.
Dodds et al. (2016)	395 pregnant women with GDM and 1,925 controls in Nova Scotia and Quebec, October 2002-July 2005	Nested case-control study	Explored the association between 25(OH)D concentration and GDM and determined if there was an interaction between smoking and 25(OH)D.	Confirms an inverse association of vit. D status with GDM risk, particularly among women who smoke during pregnancy.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Domaracki et al. (2016)	207 pregnant women, of which 171 with pregnancy-related complications and 36 women with normal pregnancies, 2013-2015	Observational study	Examine concentrations of 25(OH)D in Polish women with normal pregnancies and pregnancies complicated by gestational hypertension, preeclampsia or GDM.	25(OH)D deficiency is common among pregnant Polish women.
Eckhardt et al. (2014)	2,473 mother-child pairs, 1959-1965	Multi-centre cohort study	Examine the association between maternal vit. D status and infant anthropometry	Low maternal vit. D status was associated with deficits at birth in infant weight and BMI that were recouped across the first year of life. Associations with reduced measures of linear and skeletal growth were sustained from birth to 12 months.
Flood-Nichols et al. (2015)	235 pregnant women, 2014	Retrospective cohort study	Analyze the relationship between vit. D deficiency in the first trimester and subsequent clinical outcomes.	vit. D deficiency did not associate with adverse pregnancy outcomes. There was a high prevalence of vit. D deficiency in young, reproductive -aged women.
Halicioglu et al. (2011)	258 healthy pregnant women in Izmir, Turkey, March 2008-May2008	Prospective cohort	Measure serum 25(OH)D concentrations of pregnant women in their last trimester and their neonates at delivery to determine the factors associated with maternal serum 25(OH)D concentrations.	Despite a sunny environment, vit. D deficiency and insufficiency are highly prevalent among mothers and their neonates, generally due to the life style and nutritional status of mothers.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Hollis et al. (2011)	350 pregnant women in South Carolina, January 4, 2004-July 31, 2009	Double blind randomized clinical trial	Examine maternal/neonatal circulating 25(OH)D levels at delivery, with secondary outcomes 25(OH)D ≥32 ng/ml achieved and 25(OH)D concentration required to achieve maximal $1,25(OH)_2D$ production.	vit. D supplementation of 4,000 IU/day for pregnant women was safe and most effective in achieving sufficiency in all women and their neonates regardless of race while the current estimated average requirement was ineffective at achieving adequate 25(OH)D levels, especially among African Americans.
Huang et al. (2013)	658 pregnant women, 1996-2008	Prospective cohort study	Assessed whether self-reported maternal birthweight was associated with risk of early pregnancy vit. D deficiency.	There is a relationship between maternal birthweight and risk of vit. D deficiency during early pregnancy.
Huang et al. (2014)	498 pregnant women in Seattle, Washington, April 2009-Decmeber 2010	Cross-sectional study	Evaluate the association between early pregnancy 25(OH)D levels and antepartum depression and anxiety symptoms and potential modifiers.	There is modest evidence for inverse cross-sectional associations of early pregnancy maternal vit. D levels with antepartum depression symptoms. These associations may be modified by physical activity.
Josefson et al. (2016)	360 pregnant women, July 2000-April 2006	Prospective observational	Examine associations between maternal BMI and maternal and cord blood levels of 25(OH)D in full term neonates born to single racial cohort residing at similar latitude and examine associations between maternal glucose tolerance with maternal levels of 25(OH)D and the relationship between cord blood 25(OH)D levels and neonatal size.	Maternal levels of 25(OH)D are associated with maternal BMI.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Lechtermann et al. (2014)	63 pregnant women at delivery, January 2005-December 2008	Prospective cohort	Investigate the influence of season on maternal vit. D status and placental vit. D metabolism.	Women with preeclampsia displayed lower vit. D levels in response to seasonal changes.
Lindsay et al. (2015)	100 pregnant women with BMI 30.0-39.9 kg/m², March-November 2012	Prospective observational study	Assess maternal dietary and lifestyle habits in an obese cohort to identify priority areas to be addressed in future studies and in clinical practice.	Macronutrient intakes among obese pregnant women were not compliant to healthy eating guidelines, intakes of calcium, iron, folate and vit. D were poor from diet alone.
Liu et al. (2017)	98 pregnant women with GDM in Beijing, October 2013-July 2015	Case-control study	Study the vit. D nutritional status of pregnant women with GDM in the middle and late pregnancy and analyze the different sources of vit. D intake.	20.45% of pregnant women with GDM in their middle and late pregnancy are deficiency in vit. D though their vit. D levels were higher than the general population.
Lundqvist et al. (2016)	184 pregnant women in Northern Sweden, September 2006-March 2009	Longitudinal	Assess vit. D status during pregnancy and postpartum and identify the factors associated with vit. D status in pregnant women.	Gestational and postpartum week, season, dietary intake of vit. D and vitamin supplementation were all significantly associated to plasma 25(OH)D levels.
Luque-Fernandez et al. (2013)	2,583 non-Hispanic Black and White women, 1995-2008	Prospective cohort	Evaluate seasonal variation of 25(OH)D among pregnant women, focusing on patterns and determinants of variation.	Non-Hispanic Black women had lower average 25(OH)D concentrations throughout the year and smaller seasonal variation levels compared to non-Hispanic White women.
McGowan et al. (2011)	64 pregnant women, years not specified	Prospective observational study	Determine dietary intakes of vit. D throughout pregnancy.	Main food groups contributing to vit. D intake were meat (oily fish), eggs and breakfast cereals. Oily fish is the best dietary source of vit. D.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
McDonnell et al. (2017)	1,064 pregnant women, September 2015-December 2016	Prospective cohort study	Determine if the reported inverse relationship between maternal 25(OH)D and preterm birth risk could be replicated at the Medical University of South Carolina, treating a large, diverse population.	Maternal 25(OH)D levels ≥40 ng/ml were associated with substantial reduction in preterm birth risk in a large, diverse population of women.
Mir et al. (2017)	87 pregnant women, 2013	Open-label, parallel group, prospective randomized and controlled trial	Assess the efficacy and safety of various doses of vit. D during pregnancy.	Starting at 16 weeks of gestation, vit. D supplementation of 2,000 IU per day or the monthly equivalent dose is more effective in achieving higher vit. D levels throughout pregnancy without an increase in the risk of toxicity to the mother or neonate.
Mirzakhani et al. (2016)	816 pregnant women, 2009-2013	Nested case-control study	Assessed the effect of vit. D supplementation, initiated in early pregnancy, on the development of preeclampsia.	vit. D supplementation initiated in weeks 10-18 of gestation did not reduce preeclampsia incidence. vit. D levels ≥30 ng/ml at trial entry and in late pregnancy were associated with a lower risk of preeclampsia.
Moller et al. (2012)	153 healthy Caucasian women with pregnancy plans and 75 non-pregnant, age-matched women in Aarhus, Denmark, October 2006-Jnaury 2008	Population-based controlled cohort study	Study the effects of pre-conception 25(OH)D levels on chances for pregnancy as well as the effects of 25(OH)D during pregnancy on the risk of miscarriage, birthweight and length, Apgar score and head circumference.	25(OH)D levels did not affect fertility or pregnancy outcomes, although low 25(OH)D levels may be associated with an increased risk of late miscarriage.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Morisset et al. (2016)	1,186 pregnant women in Canada, 2008-2011	Prospective cohort	Examine iron, vit. D, and calcium intakes from diet and supplements in relation to maternal characteristics.	Among Canadian women, the probability of having lower iron, vit. D and calcium intakes is higher among those born outside Canada; supplement intake is a major contributor to total iron and vit. D intakes; and higher education level and age over 30 years are associated with supplement intake.
Neilsen et al. (2013)	605 women with postpartum depression and 875 controls in Danish women,	Nested case-control study	Determine whether low vit. D status during pregnancy was associated with postpartum depression.	No association between low maternal vit. D levels during pregnancy and risk of postpartum depression. It is noted that an increased risk of postpartum depression was found among women with the highest vit. D concentrations.
O'Brien et al. (2017)	334 pregnant women in Dublin, Ireland, 2007-2011	Secondary data analysis of a randomized control trial	Determine if exposure to winter and low maternal 25(OH)D levels in early pregnancy were associated with maternal glucose metabolism.	Women who attended their first antenatal visit during the months of extended winter were more likely to have raised insulin resistance in early pregnancy, which had a lasting association to 28 weeks, and was independent of 25(OH)D levels.
Oliver et al. (2014)	12,049 pregnant women, October 2005-February 2010	Collaborative, multi-center birth cohort	Assess maternal dietary habits across Europe during pregnancy in relation to their national pregnancy recommendations.	Maternal dietary habits during pregnancy varies significantly across Europe and may be influenced by national recommendations.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Pratumvinit et al. 2015	147 Thai pregnant women, September 2011-January 2012	Cross sectional	Determine the vit. D status in pregnant women and examine the factors associated with vit. D deficiency.	vit. D deficiency is common among pregnant Thai women. The prevalence of vit. D deficiency is increased in women who have a lower pre-pregnancy BMI and who's 25(OH)D levels were collected in the winter.
Rezavand et al. (2016)	120 healthy pregnant women and 120 women who had preeclampsia, 2014	Case-control study	Compare the serum levels of vit. D and interleukin-6 in healthy pregnant women with those with preeclampsia	Inflammatory factors and cytokines such as interleukin-6 can be considered as risk factors for preeclampsia.
Ringrose et al. (2011)	78 participants with hypertension and 109 controls, September-October 2008 and January-March 2009	Case-control study	Examine the association between vit. D status and hypertension in late pregnancy.	There is a high prevalence of vit. D deficiency in pregnant women recruited in Saskatoon, Saskatchewan. Women with low circulating vit. D concentrations are more likely to have hypertension.
Rodriguez et al. (2016)	2,036 pregnant women in Spain, November 2003-February 2008	Population-based cohort study	Prevalence and determinants of vit. D insufficiency and deficiency in pregnancy.	vit. D insufficiency and deficiency are highly prevalent in pregnancy.
Roth et al. (2012)	34 non-pregnant and 27 pregnant women in Dhaka, Bangladesh, July 2009-February 2010	Double blind randomized clinical trial	Generate preliminary pharmacokinetic and safety data to inform the design of supplementation regimens for use in future larger-scale trials of antenatal vit. D supplementation in Bangladesh.	The response to a single 70,000 IU dose of vit. D3 was similar in pregnant and non-pregnant women and consistent with previously studies in non-pregnant adults.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Song et al. (2013)	125 pregnant women in Beijing, December 2010-February 2011	Longitudinal study	Assess the vit. D status of pregnant women residing in Beijing in winter and evaluate the impact of maternal factors on 25(OH)D levels.	Pregnant women in Beijing are at very high risk of vit. D deficiency in winter, duration of sun exposure and use of multivitamin were the most important, determinants for vit. D status.
Tian et al. (2016)	2,558 pregnant women, 1996-2008	Nested case-control study	Investigate associations between maternal serum 25(OH)D levels and infant birthweight for gestation age, including potential effect modification by maternal race/ethnicity and infant sex.	Maternal serum concentrations of 25(OH)D in early and mid-pregnancy were positively associated with birthweight for gestational age among non-Hispanic Black male and female infants and non-Hispanic White male infants.
Wang et al. (2016)	20 women undergoing primary miscarriage, 20 women with recurrent miscarriage, 20 women with normal pregnancy in Xi'an Jiaotong, China, October 2013-October 2014	Observational study	Investigate the expression of 25-hydroxyvitamin D_3-1α-hydroxylase at the fetal-maternal interface in the first trimester pregnancy and to determine whether 25-hydroxyvitamin D_3-1α-hydroxylase was associated with recurrent miscarriage.	Women with recurrent miscarriage have a lower level of 25-hydroxyvitamin D_3-1α-hydroxylase expression in chorionic villi and decidua compared with normal pregnant women.
Xioa et al. (2015)	5,823 pregnant women from January 2011-June 2012	Cross sectional observational study	Evaluate vit. D status of women in Eastern China during the second trimester of pregnancy.	There is a high prevalence of vit. D deficiency among pregnant Chinese women and 25(OH)D levels varied according to season and air temperature.

Author	Population/Duration of Study	Type of Study	Aim	Major Findings
Yu et al. (2013)	90 pregnant women with preeclampsia and 1,000 unaffected controls, 2006-2010	Case-Control study	Determine whether the maternal serum levels of vit. D in the first trimester of pregnancy are altered in cases that develop preeclampsia and whether the levels are related to biochemical and biophysical markers of impaired placental perfusion and function.	Among pregnancies that develop preeclampsia maternal serum total vit. D levels at 11-13 weeks of gestation are not altered.
Zhao et al. (2012)	1,814 females of childbearing age, 2003-2006	Cross-sectional	Examine prevalence and correlates of vit. D deficiency and inadequacy among US women of childbearing age	Race/ethnicity other than for non-Hispanic White and obesity were associated with increased risk of vit. D deficiency, and dietary supplement use, milk consumption and sunlight exposure were associated with a decreased risk for vit. D deficiency and inadequacy, current smokers, history of diabetes and cardiovascular disease are associated with increased risk for vit. D deficiency.
Zhou et al. (2014)	2,960 pregnant women and 100 healthy controls in Guangzhou, China, September 2010-August 2011	Prospective observational study	Assess maternal 25(OH)D status and its association with pregnancy outcomes.	There were no significant differences in most adverse pregnancy outcomes among pregnant women with different levels of vit. D at 16-20 weeks of gestation except for higher prevalence of GDM and preterm delivery in women with high levels of vit. D.

25(OH)D = 25-hydroxyvitamin D
vit. D = vitamin D
BMI = Body Mass Index
GDM = Gestational Diabetes Mellitus
25(OH)D3 = 25-hydroxyvitamin D_3
$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D_2