Running Head: VITAMIN D AND BIRTH OUTCOMES IN PREGNANCY

Vitamin D and Birth Outcomes in Pregnancy

Kristen A. Sawka

The Ohio State University

College of Nursing

1. Statement of the Problem

Introduction

Vitamin D is an essential nutritional factor responsible for the absorption of calcium and phosphate, regulation of bone metabolism, and maintenance of muscle function (Pérez-López, Pasupuleti, Mezones-Holguin, Benites, Thota, Deshpande, & Hernandez, 2015). Recently, insufficient levels of vitamin D have become a public health concern, especially in pregnant females, because of its effects on obstetric outcomes and fetal development. Up to 70% of nulliparous women with singleton pregnancies were found to be vitamin D deficient, where deficiency was defined as a serum level of less than 30 ng/ml (Flood-Nichols, Tinnemore, Huang, Napolitano, & Ippolito, 2015). A deficiency of vitamin D in pregnant women has been associated with adverse pregnancy outcomes for the mother throughout pregnancy as well as the developing offspring. In addition to immediate pregnancy concerns, the effect of low maternal vitamin D levels in pregnancy may have health effects in mothers and their children throughout the birthing process and the beginning stages of life for the neonate.

Background of the Problem

Vitamin D deficiency is a problem commonly seen in young, reproductive aged women in the United States (Flood-Nichols et al., 2015). There are many factors and determinants that are involved when it comes to how much vitamin D is absorbed and synthesized by the body. Vitamin D can be absorbed from nutrients in the foods we eat, absorbed from the ultraviolet light from the sun, or supplemented synthetically through pills and multivitamins. Therefore, factors such as older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, and dietary habits all play a role in lower 25[OH]D levesl. (Mithal, Wahl, Bonjour, Burckhardt, Dawson-Hughes, Eisman, El-Hajj Fuleihan, Josse, Lips, & Morales-

Torres, 2009) These influences on vitamin D 25[OH]D levels contribute to the high risk for vitamin D deficiency among pregnant women . In a retrospective cohort study that included 310 pregnant, nulliparous women in their first trimester of a singleton pregnancy, seventy percent of the participants were found to be deficient in vitamin D (Flood-Nichols et al., 2015). However, in another study involving 2382 mothers, 31.8% and 19.6% were found to be vitamin D insufficient and deficient, respectively (Rodriguez, García-Esteban, Basterretxea, Lertxundi, Rodríguez-Bernal, Iñiguez, Rodriguez-Dehli, Tardón, Espada, Sunyer, & Morales, 2014). In this same study, it was found that an sufficient amount of circulating maternal vitamin D (25[OH]D3 $\geq$ 30 ng/ml) in pregnancy decreased the risk of needing an emergency caesarean section by obstructed labor (Rodriguez et al., 2014). From this understanding, it is becoming increasingly apparent that vitamin D insufficiency plays a role in pregnancy and birth outcomes.

Purpose of the Study

There has been conflicting research findings as to how much of an impact maternal serum vitamin D has on specific birth outcomes including birth weight, gestational age, mode of delivery, and weight gain of the mother. Furthermore, there has been little evidence regarding the exact time in pregnancy in which vitamin D serum levels have the greatest impact on birth outcomes. Therefore, the purpose of this study was to examine the effects of maternal vitamin D levels throughout pregnancy on specific birth outcomes including gestational age, birth weight, maternal weight gain and birth mode, and to identify the trimester during pregnancy in which circulating vitamin D (25(OH)D) has the greatest impact on birth outcomes.

Significance of the Study

There is conflicting evidence on whether or not vitamin D insufficiency has an effect on birth outcomes. This study can contribute further knowledge of the importance of maternal vitamin D status on the birthing process and the offspring itself. These findings will add to the literature and advance understanding of the relationship between maternal vitamin D status during pregnancy and birth outcomes. Public awareness of the importance of vitamin D and counseling of reproductive-aged females can be beneficial for both the mother and fetus at these critical times in development.

Conceptual Frame of Reference (Theory)

David Barker's theory of the Developmental Origins of Health and Disease provided the framework of the investigation of maternal vitamin D status in pregnancy as a predictor of birth outcomes, ultimately influencing future health and disease. This theory explains how early factors in utero and the beginning stages of life affect one's future health. An original study in 2003 traced the history of 15,000 men and women born before 1930. 3,000 of these participants were found to have already passed away from coronary heart disease or other related conditions (Barker, 2003). According to Barker (2003) out of these 3,000 people, a high number of these deaths occurred among people who were born with a lower than average birth weight. This sparked the "fetal origins hypothesis" which proposes that under nutrition in the fetal and early infant stages of life go on to change the structure of the body, making these neonates more susceptible to cardiovascular disease later on in life. These early findings from the 20^{th} century sparked the idea that time spent in utero and the beginning months of one's life influence their overall future health into adulthood. Adverse variables in the fetal stages of life and into infancy is proven to have an associated with future adult health because of these initial studies.

Study Aims

This study will examine the effects of maternal vitamin D throughout pregnancy, at three different time points corresponding with each of the three trimesters of pregnancy. The primary aim of the study is to investigate the relationship between maternal circulating vitamin D (25(OH)D) in each of three trimesters of pregnancy and birth outcomes including birth weight, gestational age, mode of delivery, and weight gain of the mother. A secondary aim of this study is to investigate the relationship between maternal body mass index (BMI) and maternal circulating vitamin D levels with birth outcomes. Lastly, this study will aim to investigate if the season of which the pregnancy occurs has any effect on the overall maternal serum levels.

Definition of Terms

In this study, we define vitamin D levels in terms of nanomoles per liter (nmol/L). 'C' for cesarean section, 'O' for operative birth including forceps or vacuum assist, or 'V' for vaginal birth will represent the different birth mode outcomes. Vitamin D status will be measured at 3 different time points, , which will correlate with each of the three trimesters of pregnancy. Body mass index (BMI) is a measure of body fat based on height and weight. This is calculated by dividing weight (in kilograms) by height (in meters squared).

Limitations

One of the most significant limitations in the study was the size of the sample. Another limitation of this study is that this is a secondary analysis and therefore variables to examine relationships are limited to those included in the primary study designed to identify the frequency of vitamin D deficiency in pregnant women and analyze the relationship between maternal vitamin D status and placental vascular development, ultimately influencing preeclampsia risk factors and onset during pregnancy.

2. Review of the Literature (5)

Vitamin D

The primary variable we will be analyzing in this secondary analysis is a hormone synthesized in the body, known as Vitamin D (25[OH]D3). Vitamin D levels can be assessed through obtaining whole blood and using enzyme immunoassay to determine circulating serum level. Vitamin D status is affected by sun exposure, dietary intake, and supplementation. Vitamin D is synthesized in the skin when exposed to ultraviolet light from the sun (Lips, 2006). Other factors, such as clothing type, age, skin pigmentation, and the use of sunscreen also affect the amount of the vitamin D that is synthesized (van Schoor & Lips, 2011). Overall sun exposure in relation to location and total minutes of sun exposure an area receives has an influence on overall vitamin D level. This can also vary based on the season during which vitamin D levels are being measured. When sun exposure is limited, one must use other means make up for the deficiency either through supplementation or dietary intake, primarily fatty fish such as herring or mackerel which are not recommended to be eaten in large amounts during pregnancy (Lips, 2006).

One of the most important roles of vitamin D is to maintain extracellular calcium ion levels in the body by controlling the amount of calcium that is absorbed from the small intestine (Mithal et al., 2009). If vitamin D is low, thus making calcium levels low, the parathyroid hormone (PTH) regulates and mobilizes the calcium from stores, specifically the bones, to increase the amount of calcium in blood (Lips, 2006). A substantial amount of circulating vitamin D and calcium, would then suppress the parathyroid hormone (PTH). Even though there are compensation mechanisms throughout the body, adequate amounts of vitamin D are necessary for the proper absorption and regulation of calcium.

Vitamin D Metabolism

Vitamin D goes through two conversions in the body. The first occurs in the liver, where vitamin D3, also known as cholecalciferol, is hydroxylated into 25-hydroxyvitamin D

(25(OH)D) by the enzyme 25-hydroxylase CYP2R1 (Lips, 2006). This vitamin D serum level (25[OH]D) is the form of vitamin D found and measured in the circulating blood. The second conversion in the kidneys converts 25-hydroxyvitamin D (25(OH)D) into 1,25-dihydroxyvitamin D (1,25(OH)2D) via the enzyme CYP27B1, which is the active metabolite responsible for stimulating the calcium absorption in the gut (Lips, 2006). The circulating form of vitamin D, 25[OH]D is used as the clinical measure of vitamin D status and has been associated with health effects (Mithal et al., 2009).

There are health consequences for severe vitamin D deficiency including rickets or osteomalacia (Lips, 2006). Furthermore, even mild vitamin D insufficiency may cause bone resorption, osteoporosis, and fractures, especially in high risk groups. High-risk groups include young children, pregnant women, the elderly, and immigrants (Lips, 2007). There is consensus that vitamin D is essential for the overall healthy growth and development of bones, muscles, and teeth. There is emerging evidence for the association of vitamin D throughout pregnancy in the prevention of adverse birth outcomes.

Vitamin D in Pregnancy

Pregnant women are among the risk groups for having vitamin D deficiency (van Schoor & Lips, 2011). In a study by Flood-Nichols (2015), seventy percent of the participants (n=235) were found to be vitamin D deficient. Deficiency was defined as a serum concentration of less than 30 ng/ml. A low vitamin D status has been increasingly associated with various adverse pregnancy outcomes and fetal development, such as decreased birth weight, length and gestational age at birth (Pérez-López et al., 2015). As the fetus is dependent of the mother for its vitamin D source through placental transfer, maternal vitamin D is a key determinant in vitamin D status. It is suggested that as much as 4000IU/day of vitamin D in pregnant women and 6400

IU/day for lactating women is an effective amount to improve the health of the mother, fetus, and in the future, the breastfeeding infant (Pludowski, Holick, Pilz, Wagner, Hollis, Grant, Shoenfeld, Lerchbaum, Llewellyln, Kienreich, & Soni, 2013).

Vitamin D and Infant Birth Outcomes

Recent findings suggest a relationship between maternal vitamin D status during pregnancy and newborn birth outcomes including birth weight and length of the neonate. In a systematic review and meta-analysis of randomized controlled trials involving pregnant women and neonates, birth weight and birth length were significantly greater for the neonates of the mothers receiving vitamin D supplementation (Pérez-López et al., 2015). The vitamin D supplementation was associated with an increase of circulating 25(OH)D levels in the mothers. Conversely, a study measuring the serum 25(OH)D levels of 2382 mother and children found no association between maternal circulating 25(OH)D and birth weight and length (Rodriguez et al., 2014). However, this study did find that mothers with a vitamin D serum concentration of less than 37.5 nmol/L tended to have a lower birth weight. Rodriguez et al., (2014) concluded that mothers with a higher vitamin 25(OH)D serum concentration tended to have neonates with a smaller head circumference, however this was not found to be statistically significant. They also found no association between maternal circulation 25(OH)D concentration and small for gestational age (SGA) and fetal growth restriction (FGR) (Rodriguez et al., 2014). On the contrary, another study of 995 singleton pregnancies found that a higher infant birth weight was associated with a higher maternal BMI and consequently, a lower vitamin D 25[OH]D level (Savvidou, Makgoba, Castro, Akolekar, & Nicolaides, 2012). Some of the inconsistencies in the study could be explained by selection bias and the small rate of adverse pregnancy outcomes. In this study, they were not able to gather a circulating serum level from all of the participants, and there was a small number of adverse pregnancy outcomes in this specific group.

Vitamin D and Risk of Birth Mode

Recent findings suggest conflicting evidence between maternal vitamin D status during pregnancy and adverse birth mode including operative birth and cesarean section. Pérez-López et al., (2015) reported no association between increased circulating 25(OH)D levels and cesarean section. Another recent study, measuring first trimester serum 25(OH)D levels in 995 women, found no significant difference in serum level of those women who delivered vaginally and by those who delivered by either elective or emergency caesarean section (Savvidou et al., 2012). However, a prospective cohort study found that females with sufficient circulating vitamin D serum levels (greater than or equal to 30 ng/ml), had lower risk for caesarean section due to obstructed labor (non-elective or non-emergency) (Rodriguez et al., 2014). Some of the variables that might explain these discrepciences include: different measurement tools of vitamin D levels, diverse patient populations, varying sample sizes, and interventions offered. Because of this conflicting evidence, it apparent that further research needs to be done on the exact role vitamin D plays in regards to birth mode.

Vitamin D and Maternal Weight

There has been evidence that indicate as maternal weight increases, vitamin D 25[OH]D serum levels decrease. Savvidou et al., (2012) reported that as BMI increased, maternal serum 25(OH)D decreased. In another study, there was no found association between body mass index of the mother and vitamin D serum level (Flood-Nichols et al., 2015). Some of these discrepancies could have been due to the fact that BMI is not a perfect indicator of whether a person is overweight or obese because it does not take into account muscle mass of each individual person.

Summary

Vitamin D is an essential hormone needed by the body for many conversions and developments throughout one's lifespan. It has been identified that females are among the at risk groups for vitamin D deficiency especially during pregnancy. Overall there has been conflicting evidence as to the effects of maternal weight and gestational weight gain throuhgout pregnancy association with vitamin D serum levels. There has also been conflicting evidence of the effect of these low vitamin D levels on infant birth weight, gestational age and birth modes. This secondary analysis was designed to determine the influence of maternal vitamin D on these variables as well as the time during pregnancy in which vitamin D serum level has the greatest effect on these outcomes.

3. Methodology

Introduction

Vitamin D deficiency among reproductive-age women has been identified as common problem seen in the United States (Flood-Nichols et al., 2015). This type of deficiency during pregnancy may have an influence on various adverse birth outcomes. The purpose of this study was to examine the effects of maternal vitamin D levels throughout pregnancy on specific birth outcomes such as gestational age, birth weight, and birth mode, and to identify the trimester during pregnancy in which circulating vitamin D (25(OH)D) has the greatest impact on birth outcomes. We will address three specific aims in this secondary analysis. The first aim of the study is to investigate the relationship between maternal circulating vitamin D (25(OH)D) in each of three trimesters of pregnancy with birth outcomes including birth weight, maternal weight gain, gestational age, mode of delivery, and weight gain of the mother. The second aim of this study was designed to investigate the relationship between maternal body mass index (BMI) and maternal circulating vitamin D levels with birth outcomes. The third aim of this study examined the season of which the pregnancy occurs and effect on the overall maternal serum 25 [OH]D levels. The results found from this study will further the understanding of the relationship between maternal vitamin D and pregnancy and birth outcomes.

This study is a secondary analysis of data designed to examine the relationship between maternal vitamin D status and placental vascular development in the primary study. The primary study aims were to identify the frequency of vitamin D deficiency in pregnant women and analyze the relationship between maternal vitamin D status and placental vascular development, ultimately influencing preeclampsia risk factors and onset during pregnancy.

Research Design

The secondary study used a descriptive, correlational design to examine the relationships among maternal vitamin D serum level, birth weight, gestational age, mode of delivery, maternal BMI, and maternal weight gain over the three trimesters of pregnancy. Pregnancy outcome measures include maternal early pregnancy weight, maternal weight gain across pregnancy, gestational duration, mode of delivery and infant birth weight.

Population and Sample

Women interested in the primary study were recruited through advertisements placed around the community and selected based on meeting inclusion and exclusion criteria. The inclusion criteria included women with no prior deliveries (para 0, nulliparous) and a singleton pregnancy of less than 14 completed weeks of gestation. The women selected for this study also had to be over the age of 18, since women under 18 years had maternal nutritional demands that could confound the results. English speaking was required. Exclusion criteria included prior completed pregnancy, women less than 18 years of age, women with a multi-gestational pregnancy, and women whose pregnancies terminate within 20 weeks of gestation. Subjects selected to participate in the study and completed all three visits received $75 in gift cards.

Data Collection Procedures

In the primary study, women with a singleton, nulliparous pregnancy that met the inclusion criteria participated in three data collection appointments. Data collection by the research team was carried out after training by the principle investigator. In the initial visit, written consent was obtained. The initial visit included height measurements and collection of demographic information. In all three of the visits, venipuncture to collect blood samples and nutritional information was also completed. The appointments were set up at three different pregnancy time points: time 1 (10- 14 weeks gestation), 2 (22-26 weeks gestation) and 3 (32-36 weeks gestation). After the participant delivered, medical record abstraction was completed to collect pertinent health, pregnancy and birth outcomes.

Instrumentation

At each 3 data collection points, participants provided a blood sample of 45 milliliters that was obtained through venipuncture. These blood samples were tested for serum indicators of vitamin D (25[OH]D) at each of the three different time points. This was assessed using Immunodiagnostic Systems LTD (IDS) 25-Hydroyxy Vitamin D enzyme-immunoassay (EIA) to quantify the amount of calcidiol in each of the serum samples. To dissociate the vitamin D from the binding protein, 1 ml of biotin solution was added to 25 μl of the serum. This mixture was then placed in a vortex for 10 seconds. A microtitre wells coated with sheep 25-OH D antibody was filled with 200 μL of the sample serum, sealed, and incubated for 2 hours at room temperature. The wells were then again incubated for another 30 minutes at room temperature after adding an enzyme to selectively bind to the Vitamin D-biotin complex. After each of the incubations, the wells were washed using WASHBUF. Lastly, a chromogenic substrate and a hydrochloric said solution was added to the samples. After 30 minutes, the color intensity of the stopped reactions in each well were able to inversely determine the 25-OH D concentration of each sample.

Human Subjects

The investigator of the primary study obtained IRB approval to use human subjects including for this study. All staff and volunteers working with study have completed education on protection of human subjects. The research team was involved in the recruitment of volunteers, data collection, analysis and dissemination.

Data Analysis

Descriptive analysis including mean, standard deviation, and ranges were used to determine vitamin D serum levels for the sample in each three of the time points. The relationship between maternal circulating 25[OH]D levels and birth mode, gestational duration and infant birth weight were analyzed using regression models, controlling for maternal early pregnancy weight and weight gain. Significance was determined at $p<0.05$. To assess the relationship between vitamin D levels and birth mode we used a dichotomous variable, 1 for the birth mode 'C' for Cesarean and 0 if the birth mode was vaginally, 'V' or 'O', operative assist. To assess the relationship between vitamin D levels and childbirth weight, we created three linear regression equations for each three of the time points. To assess the relationship between vitamin D serum levels and gestational age we also created three linear regression equations for each of the three time points. All three of the regressions completed were controlled for maternal first weight and weight gain.

4. Results

Sample Descriptive Statistics

In this secondary analysis, we analyzed the sample used in the primary study involving 52 nulliparous women over the age of 18 with singleton pregnancies. The mean early pregnancy weight and weight gain for the sample size was 169 and 29.7 pounds respectively. The average vitamin D serum level for trimester1 was 63.3 nmol/L and ranged from 41.6 to 123.5 nmol/L. The average vitamin D serum level for trimester 2 was 65.7 and ranged from 36.5 to 154.3 nmol/L. The average vitamin D serum level for trimester 3 was 65.9 nmol/L and ranged from 25.3 to 182.8 nmol/L. The mean for gestational age of the infant was 274.3 days of gestation and the mean for infant birth weight was 3311 grams.

Table 1. Distributions of the continuous variables of interest:

	Sample size	Mean	STD	Median	Minimum	Maximum
Trimester1	52	63.3	19.5	56.7	41.6	123.5
Trimester2	51	65.7	20.4	62.8	36.5	154.3
Trimester3	51	65.9	24.4	60.8	25.3	182.8
Gestation Age	52	274.3	10.3	276.0	238.0	289.0
Infant Birth Weight	52	3311	549.2	3355	1429	4774
Early Pregnancy Weight	50	169.0	35.1	165.0	117.0	289.8
Late Pregnancy Weight	51	198.5	36.0	191.2	152.0	307.3
Weight Gain	50	29.7	11.7	27.5	11.4	64.0

Vitamin D and Birth Mode

Participants who had a cesarean birth had the lowest vitamin D levels in all three time points throughout pregnancy. The mean vitamin D levels between the operative and vaginal birth were comparable, however the average vitamin D levels for each three time points for operative birth participants appeared to be slightly higher than the respective levels for the participants who gave birth vaginally.

Table 2. Distribution of vitamin D as a function of birth mode:

	Birth Mode											
	C				O				V			
	Sample size	Mean	STD	Median	Sample size	Mean	STD	Median	Sample size	Mean	STD	Median
Time1	10	55.0	15.3	46.7	9	68.8	21.6	59.0	33	64.3	19.8	57.1
Time2	10	58.7	18.3	56.2	9	67.4	24.5	69.7	32	67.4	20.0	63.2
Time3	10	55.4	20.6	50.9	9	71.3	26.5	69.7	32	67.6	24.7	62.2

(c = cesarean birth, o = operative birth, v = vaginal birth)

Spearman correlation was used to determine if a relationship exists between maternal vitamin D serum level, early pregnancy weight, gestational weight gain, and birth mode. The outcome measures for birth mode included operative birth, vaginal, or cesarean section. We found no correlation between first trimester vitamin D levels or maternal gestational weight gain and birth mode. Therefore, we found no significant correlation between vitamin D serum levels and birth mode, specifically related to cesarean section.

Early Maternal Weight and Maternal Circulating Vitamin D

When assessing for a relationship between vitamin D levels in each of the three trimesters, early maternal weight, and gestational weight gain, a strong negative correlation (r, -0.48; $p < 0.001$) between maternal circulating vitamin D 25[OH]D in the first trimester of pregnancy and maternal early pregnancy weight was identified.

Vitamin D, Infant Birth Weight and Gestational Age

We found no correlation between vitamin D levels at any of the three trimesters of pregnancy and gestational age or infant birth weight. All p-values were greater than 0.514.

Table 3. Vitamin D, Gestational Age at Birth, and Infant Birth Weight

	25[OH]D (nmol/L)		
	1st Trimester	2nd Trimester	3rd Trimester
Gestational Age at Birth	$R^2 = 0.03$ p = 0.827	$R^2 = 0.03$ p = 0.756	$R^2 = 0.03$ p = 0.642
Infant Birth Weight	$R^2 = 0.13$ p = 0.514	$R^2 = 0.11$ p = 0.891	$R^2 = 0.11$ p = 0.887

Early Maternal Weight and Birth Mode

Spearman correlation was used to determine the association between early maternal weight and birth mode. There was a significant association between maternal early pregnancy weight and risk of cesarean section (OR = 1.027, p = 0.0416).

Table 4. Vitamin D and Birth Mode

	Vitamin D 1st Trimester	Maternal Early Pregnancy Weight	Maternal Gestational Weight Gain
Mode of Delivery	OR = 0.993 p = 0.819	OR = 1.027 p = 0.0416	OR = 0.998 p = 0.9439

(OR = odds ration, p = p-value)

5. Conclusions and Recommendations

Summary of Findings

In summary, we found no significant associations between vitamin D serum levels and gestational age at birth or infant birth weight. We did however find a strong correlation between early maternal pregnancy weight and vitamin D serum levels in the first trimester. The correlation was a strong, negative correlation. There was no association between vitamin D serum levels in any of the three trimesters of pregnancy and birth mode. However, there was a strong correlation between early maternal pregnancy weight and greater odds of cesarean delivery

Implications of this Study

Knowing the effects of maternal vitamin D on pregnancy and birth outcomes can aid to promote healthy pregnancies, labor experiences, and birth outcomes for both the mother and infant involved. Further investigation is needed to determine the exact amount of circulating maternal vitamin D levels to be obtained, to assist in preventing unsafe pregnancies and birthing outcomes. Further research with larger sample sizes to pinpoint the exact role and magnitude maternal vitamin D levels play in pregnancy and birth outcomes would complement existing evidence on the importance of vitamin D on overall health and well being.

Recommendations

After analyzing the results from this study, it is apparent that nutritional counseling to promote optimal weight not only during pregnancy, but also before pregnancy may promote ideal pregnancy outcomes in regards to birth mode.

References

Barker, D. (2003). The midwife, the coincidence, and the hypothesis. *BMJ: British Medical Journal, 327*(7429), 1428-1430.

Flood-Nichols, S. K., Tinnemore, D., Huang, R. R., Napolitano, P. G., & Ippolito, D. L. (2015). Vitamin D Deficiency in Early Pregnancy. *PLoS ONE*,*10*(4), e0123763. http://doi.org/10.1371/journal.pone.0123763

Lips, P. (2006). Vitamin D physiology. *Progress in Biophysics and Molecular Biology, 92*(1), 4-8. doi:http://dx.doi.org.proxy.lib.ohio-state.edu/10.1016/j.pbiomolbio.2006.02.016

Lips, P. (2007). Relative value of 25(OH)D and 1,25(OH)2D measurements. *Journal of Bone and Mineral Research, 22*(11), 1668-1671. doi:10.1359/jbmr.070716

Mithal, A., Wahl, D. A., Bonjour, J., Burckhardt, P., Dawson-Hughes, B., Eisman, J. A., . . . Morales-Torres, J. (2009). Global vitamin D status and determinants of hypovitaminosis D. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 20*(11), 1807-1820. doi:10.1007/s00198-009-0954-6

Pérez-López, F. R., Pasupuleti, V., Mezones-Holguin, E., Benites-Zapata, V. A., Thota, P., Deshpande, A., & Hernandez, A. V. (2015). Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: A systematic review and meta-analysis of randomized controlled trials. *Fertility and Sterility, 103*(5), 1278-1288.e4. doi:http://dx.doi.org.proxy.lib.ohio-state.edu/10.1016/j.fertnstert.2015.02.019

Pludowski, P., Holick, M. F., Pilz, S., Wagner, C. L., Hollis, B. W., Grant, W. B., . . . Soni, M. (2013). Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—A review of recent evidence. *Autoimmunity Reviews, 12*(10), 976-989. doi:http://dx.doi.org.proxy.lib.ohio-state.edu/10.1016/j.autrev.2013.02.004

Rodriguez, A., García-Esteban, R., Basterretxea, M., Lertxundi, A., Rodríguez-Bernal, C., Iñiguez, C., . . . Morales, E. (2015). Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. *BJOG: An International Journal of Obstetrics & Gynaecology, 122*(12), 1695-1704. doi:10.1111/1471-0528.13074

Savvidou, M. D., Makgoba, M., Castro, P. T., Akolekar, R., & Nicolaides, K. H. (2012). First-trimester maternal serum vitamin D and mode of delivery. *British Journal of Nutrition, 108*(11), 1972-1975. doi:10.1017/S0007114512000207

Schoenmakers, I., Pettifor, J. M., Peña-Rosas, J., Lamberg-Allardt, C., Shaw, N., Jones, K. S., . . . Bouillon, R.Prevention and consequences of vitamin D deficiency in pregnant and lactating women and children: A symposium to prioritise vitamin D on the global agenda. *The Journal of Steroid Biochemistry and Molecular Biology,* doi:http://dx.doi.org.proxy.lib.ohio-state.edu/10.1016/j.jsbmb.2015.11.004

van Schoor, N. M., & Lips, P. (2011). Worldwide vitamin D status. *Best Practice & Research Clinical Endocrinology & Metabolism, 25*(4), 671-680. doi:http://dx.doi.org.proxy.lib.ohio-state.edu/10.1016/j.beem.2011.06.007

Wagner, C. L., Baggerly, C., McDonnell, S. L., Baggerly, L., Hamilton, S. A., Winkler, J., . . . Hollis, B. W. (2015). Post-hoc comparison of vitamin D status at three timepoints during pregnancy demonstrates lower risk of preterm birth with higher vitamin D closer to delivery. *The Journal of Steroid Biochemistry and Molecular Biology, 148*, 256-260. doi:http://dx.doi.org.proxy.lib.ohio-state.edu/10.1016/j.jsbmb.2014.11.013