Calcium and Vitamin D Nutrition during Pregnancy:

A Survey of Family Physicians and a Chart Review of Pregnant Women

with Gestational Diabetes Mellitus

By

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Abstract

Introduction: Adequate calcium and vitamin D are needed for maternal and fetal health. Many pregnant women are not consuming enough calcium and are at high risk for vitamin D deficiency.

Objectives: To 1) investigate the nutrition-related knowledge, opinions, and clinical practices of family physicians (FPs) towards prenatal calcium and vitamin D; and 2) determine the prevalence of meeting a predefined cut-off serum 25-hydroxyvitamin D concentration ([25-OHD]) for vitamin D sufficiency ($\geq$ 75 nmol/L) in a cohort of pregnant women with gestational diabetes mellitus (GDM).

Methods: Part 1: 500 surveys were mailed out to randomly selected FPs across Manitoba. Part 2: data were collected via retrospective chart review of 35 pregnant women with GDM attending a teaching hospital in Winnipeg, Manitoba between January 1, 2010 and December 31, 2013 and having one serum [25-OHD] measurement during their pregnancy.

Results: Approximately one-third of FPs are discussing calcium and vitamin D requirements and supplements with their prenatal patients. The top three perceived barriers to delivery of calcium and vitamin D advice were more urgent issues, lack of time, and forgetting to do so. The mean serum [25-OHD] was 52.5 ± 24.1 nmol/L (range 14-109 nmol/L). Over half of women (51.4%) were vitamin D deficient ([25-OHD] < 50 nmol/L), and 28.6% of women were insufficient ([25-OHD] 50-74 nmol/L).

Conclusions: Physicians would benefit from more training in nutrition. Multiple barriers exist that prevent FPs from providing calcium and vitamin D advice. Women with GDM have a high prevalence of vitamin D deficiency in our study.

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List of Abbreviations

$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3
25-OHD	25-hydroxyvitamin D
25-OHase	Vitamin D-25-hydroxylase
BMI	Body mass index
BV	Bacterial vaginosis
C-section	Caesarean section
CDA	Canadian Diabetes Association
CI	Confidence interval
CPG	Clinical Practice Guidelines
FPs	Family physicians
GA	Gestational age
GBS	Group B streptococcus
GDM	Gestational diabetes mellitus
g	grams
HbA1c	Glycated hemoglobin
HOMA-IR	Homeostasis model assessment of insulin resistance
hr	hour
HTN	Hypertension
IGT	Impaired glucose intolerance
IOL	Induction of labour
IQR	Interquartile range
IU	International Units

L	Litre
lbs	pounds
LC-MS/MS	Liquid chromatography-tandem mass
mg	milligrams
n	number
NICU	Neonatal intensive care unit
nmol	nanomoles
OGTT	Oral glucose tolerance test
OR	Odds ratio
OTC	Over the counter
PG	Plasma glucose
PTH	Parathyroid hormone
PTHRP	Parathyroid hormone receptor proteins
QISCI	Quantitative insulin sensitivity check index
RCT	Randomized control trial
RD	Registered dietitian
RDA	Recommended Dietary Allowance
RR	Relative risk
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
UVB	Ultraviolet B
VDBP	Vitamin D binding protein
vs	versus

WHO   World Health Organization

Chapter 1: Introduction

1.1. Overview

Nutrition is integral throughout the lifespan, especially during pregnancy. It is well known that calcium and vitamin D are required for both the development and maintenance of skeletal health.[1] Inadequate consumption of dietary calcium during pregnancy places the mother at an increased risk for gestational complications including preeclampsia, preterm delivery and excessive bone loss.[2]

Recent evidence recognizes the importance of the non-classical roles of vitamin D in pregnancy, including gestational diabetes mellitus (GDM), preeclampsia, bacterial vaginosis, and birth weight.[3] Children born to mothers who had insufficient vitamin D concentrations during pregnancy may have long-term implications including a higher risk of autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, and inflammatory bowel disease.[4]

Despite food fortification, vitamin D deficiency continues to be a problem for pregnant women in Manitoba.[5] This can be attributed to the latitude, limited sun and skin exposure, and dark skin pigmentation of many women.[6] Recently, age has been proposed as a potential risk factor for vitamin D deficiency as well.[7]

In 2010, the Institute of Medicine updated the dietary reference intake for calcium; however, the required daily amount of vitamin D and the definition of adequacy and cut off for deficiency are not clear. [1,6,8,9]

Unfortunately, the majority of Canadian women are not meeting the Recommended Dietary Allowance for calcium[10] and are at high risk for vitamin D deficiency[11], yet routine screening is not recommended in Manitoba.[12]

Family physicians (FPs) are trained to take care of most health care needs, including prenatal medical care.[13] They are expected to be able to identify women who are at risk for and to treat basic nutritional deficiencies including vitamin D deficiency.[14] FPs can refer their prenatal patients to endocrinologists for the management of GDM. Pregnant women with GDM receive nutrition counselling by the clinic's registered dietitian (RD) whereby education on calcium and vitamin D intake is provided. Based on the dietary assessment from the RD, and the presence of risk factors for vitamin D deficiency, serum 25-hydroxyvitamin D ([25-OHD]) tests can be ordered by the endocrinologist. Treatment for deficiency may be prescribed by the endocrinologist. Dietary intakes and lab work results are often recorded in patient charts.

Despite the utmost importance of adequate calcium and vitamin D during pregnancy, very limited information exists in the literature that addresses the knowledge, opinions, and clinical practices regarding calcium and vitamin D nutrition among primary care providers, including FPs.

The results from this study will help to identify what barriers exist to giving calcium and vitamin D advice, as well as document the vitamin D status, determine associations between serum [25-OHD] and glycemic control, and to determine the impact of maternal factors on serum [25-OHD] in women with GDM.

1.2. Research objectives

This research intends to address the following objectives to enhance the knowledge of nutrition care in pregnancy from the perspective of practicing FPs in Manitoba:

1. To investigate the nutrition-related knowledge, opinions, and clinical practices of FPs towards prenatal calcium and vitamin D.

2. To determine what barriers exist in providing calcium and vitamin D nutrition advice to prenatal patients.

This research seeks to address the following objectives to report on the vitamin D status in a cohort of pregnant women with GDM residing in Manitoba and attending an endocrine clinic at the St. Boniface Hospital for the management of diabetes during pregnancy.

3. To determine the prevalence of meeting a predefined cut-off serum [25-OHD] for vitamin D adequacy ($\geq$ 75 nmol/L) in a cohort of pregnant women with GDM.

4. To assess serum [25-OHD] and associations of serum [25-OHD] with glycemic indices and birth outcomes.

5. To determine the impact of maternal factors on serum [25-OHD].

1.3. Research questions

This project intends to answer the following questions:

1. What are the nutrition-related knowledge, opinions, and clinical practices of FPs towards prenatal calcium and vitamin D?

2. What barriers exist in providing calcium and/or vitamin D advice to prenatal patients?

3. What is the current vitamin D status in a cohort of pregnant women with GDM who reside in Manitoba and attended an endocrine clinic at the St. Boniface Hospital for the management of diabetes during pregnancy?

4. Are there relationships between maternal serum [25-OHD] and glycemic indices or birth outcomes for women with GDM?

5. What impact do certain maternal factors (e.g. age, weight, estimated vitamin D intake) have on maternal serum [25-OHD] in women with GDM?

1.4. Chapter summary

This study was conducted in two parts. Part 1 consisted of a survey (quantitative methodology) completed by FPs. Part 2 consisted of a chart review of pregnant women with GDM residing in Manitoba and attending an endocrine clinic at the St. Boniface Hospital for the management of diabetes during pregnancy (quantitative methodology). This thesis is structured around two manuscripts and includes the following:

Chapter 2 presents a literature review of calcium and vitamin D during pregnancy, risk factors for and impact of calcium and vitamin D deficiency, overview of GDM, FPs, the survey process, and retrospective chart reviews.

Chapter 3 describes the experimental approach and methodology used in this study.

Chapter 4 presents the first manuscript, "Calcium and Vitamin D in Pregnancy: A Survey of Family Physicians".

Chapter 5 presents the second manuscript, "Serum Vitamin D Concentrations and Glycemic Outcomes in Women with Gestational Diabetes".

Chapter 6 provides additional findings from the chart review.

Chapter 7 provides a general discussion of the research for parts 1 and 2, summary,

limitations, implications of findings, and conclusion.

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Chapter 2: Literature Review

2.1. Calcium and vitamin D

2.1.1. Calcium

Calcium is the most abundant mineral in the body with about 99% of the body's calcium found in the bones and teeth. Calcium is in some foods, dietary supplements, and some medications (e.g. antacids). By the time of normal delivery, a fetus has formed 98% of its skeleton, accumulating about 30 g of calcium. Calcium is actively transported across the placenta during pregnancy.[1]

2.1.2. Calcium: Foods and supplements in Canada

Calcium must be obtained through the diet. The most common dietary sources of calcium include milk and dairy products, primarily cheese and yogurt, tofu set in calcium, orange juice fortified with calcium, fortified beverages (soy, almond, rice), salmon and sardines (with bones).[2] In a research setting, a validated food frequency questionnaire is a method to assess dietary calcium intake.[3]

Supplemental calcium is commonly sold as either calcium citrate or as calcium carbonate. Calcium carbonate is found in commercial antacids. The absorption from calcium citrate is better than that from calcium carbonate.[4] Calcium citrate does not need to be taken with a meal and is absorbed equally well when taken with or without food.[5]

2.1.3. Endogenous synthesis of vitamin D

The major source of vitamin D for adults is exposure to natural sunlight.[6] Vitamin D can be obtained from sun exposure on the skin. Pre-vitamin D_3 (7-dehydrocholesterol) is stimulated in the keratinocytes when skin is exposed to ultraviolet B (UVB) radiation from sunlight (230-313 nm) to produce cholecalciferol (vitamin D_3).

One of the most significant factors affecting the synthesis of 7-dehydrocholesterol is latitude. Countries that are situated above 40°N (including Canada) or below 40°S, during the winter months do not receive UVB radiation strong enough to elicit endogenous synthesis.[7] Manitoba's latitude extends from the 49° parallel (including Winnipeg) up to the 59° parallel (Nunalla).

It is assumed that endogenous synthesis occurs from April to October,[7] however, regions in the far north or south likely do not accommodate endogenous synthesis in spring or fall season, since UVB is reduced as a result of the zenith angle and the atmosphere.[8] Furthermore, exposure is also limited by cold temperatures that necessitate warm clothing. Individuals who are not able to be outdoors are vulnerable to vitamin D deficiency.

2.1.4. Vitamin D: Foods and supplements in Canada

There are very few natural dietary sources of vitamin D. Vitamin D_3 (cholecalciferol) is obtained in the diet from animal-based foods (e.g. oily fish) and products fortified with vitamin D.[8] It is also obtained from the ultraviolet irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. Both vitamin D_2 (ergocalciferol) and D_3 are used for food fortification and in vitamin D supplements. In Canada, many dairy products, such as milk, yogurt, and cheeses are fortified with vitamin D_3. Plant-based products including soy beverages, rice beverages, and orange juice are fortified with vitamin D_2 and D_3.[8] The fortification of milk and margarine is mandated in Canada.[9]

Supplemental sources of vitamin D are found in multivitamins and supplements containing only vitamin D at various dosages anywhere from 200 International Units (IU)

to 1,000 IU per tablet. For example, most multivitamins contain 400 IU per tablet, while vitamin D supplements are typically 200, 400 or 1,000 IU per tablet.[8] The majority of vitamin D supplements available for purchase are in the form of cholecalciferol.

In Manitoba, vitamin D can be physician prescribed in the following amounts: 10,000 D_2 or 50,000 IU D_2 tablets, and 250,000 IU D_3/mL injections (up to 5 mL in injection).

Vitamin D supplements are generally inexpensive for the consumer. A report published by the Winnipeg Regional Health Authority (2012)[10] evaluated the average cost of vitamin D supplementation. As of May 2012, the cost per 2,000 IU dose of vitamin D_3 was $0.14, and was $4.20 per 30 days. It costs $0.29 per 400 IU D_3 dose, and $8.54 per 30 days.

2.1.5. Calcium and vitamin D recommendations

The suggested daily requirements to support health have been developed by researchers at the Institute of Medicine, National Academy of Sciences. A committee of scientific experts from the Food and Nutrition Board at the Institute of Medicine reviewed the role of calcium and vitamin D. The review on calcium and vitamin D was jointly commissioned and funded by the U.S. and Canadian governments. They found the current evidence to support the role of calcium and vitamin D on bone health to be strong enough to update the guidelines. The daily amount needed to meet the requirements for 97 to 98% of the population is known as the Recommended Dietary Allowance (RDA). The RDA for calcium for women aged 14 to 18 and 19 to 50 years is 1,300 and 1,000 milligrams (mg), respectively. The requirements are the same for both pregnant and

nonpregnant females. However, the recommended intake of vitamin D in pregnant and lactating women is subject to controversy.

The Canadian Paediatric Society (2007) recommends that pregnant and lactating women take a supplement of 2,000 IU/day. This was reaffirmed January 2013.[11]

Osteoporosis Canada (2010) recommends that all healthy adults, including pregnant or lactating women, take 800 to 1,000 IU of vitamin D_3 daily.[12] For individuals at high risk for vitamin D deficiency, supplementation at doses between 800 and 2,000 IU/day is recommended, with the potential for higher doses.

The RDA for vitamin D for pregnant and lactating women aged 14 to 50 years is 600 IU/day.[5] This recommendation is determined without consideration of ethnicity, latitude, or season. The tolerable upper intake level (UL) is 4,000 IU/day.

Health Canada (2011) also recommends 600 IU/day from food and dietary supplement sources for pregnant women.[13] This amount is assumed to be obtained from a prenatal multivitamin (400 IU) as well as eating according to the *Eating Well with Canada's Food Guide* (2007), which includes 2 cups of milk/day (200 IU).[14]

The Endocrine Society (2011) recommends that pregnant and lactating women take at least 600 IU/day, and at least 1,500 to 2,000 IU/day may be needed to maintain a blood concentration of [25-OHD] above 75 nmol/L.[15] The committee proposes an upper intake of 10,000 IU/day.

Lastly, the Winnipeg Regional Health Authority (2012) suggests 2,400 IU/day for pregnant and lactating women.[10] This amount would come from vitamin D supplementation (2,000 IU) and the remaining from a prenatal multivitamin (400 IU).

2.1.6. Calcium and vitamin D intake

Data obtained from the 2004 Canadian Community Health Survey version 2.2 provides an estimate of the average calcium and vitamin D intake from food and supplements.[16] From food sources only, it is estimated that nonpregnant women aged 19 to 30 and 31 to 50 years have an average daily calcium intake of 825 and 773 mg, respectively. When accounting for both food sources and supplements, the estimated average daily intake is increased to 950 and 969 mg for women aged 19 to 30 and 31 to 50 years, respectively. This data excludes pregnant and lactating women.

It is challenging to assess the dietary intake of vitamin D because there are few foods that contain it. Data obtained from the 2004 Canadian Community Health Survey version 2.2 provides an estimate of the average vitamin D intake from food and supplements.[17] It is estimated that nonpregnant women aged 19 to 30 years and 31 to 50 years have an average dietary intake 256 IU and 332 IU, respectively. This information indicates that women are not meeting the dietary requirement of 600 IU.

It is difficult to correlate dietary intake of vitamin D with serum [25-OHD] due to the influence of sun exposure. Serum [25-OHD] concentrations are generally higher than would be predicted on the basis of vitamin D intakes alone.[8]

2.1.7. Vitamin D metabolism

Vitamin D ingested from food or supplemental sources is incorporated first into chylomicrons. The chylomicrons are absorbed into the lymphatic system and then enter the blood circulation.[15] After entry into the circulation, whether through endogenous synthesis or from foods, vitamin D_2 and D_3 can be transported free or bound to the

vitamin D binding protein (VDBP). This protein is synthesized by the liver and extends the half-life of vitamin D_2 and D_3.[18]

Vitamin D that is ingested or produced in the skin must undergo its first hydroxylation in the liver by the vitamin D-25-hydroxylase (25-OHase) enzyme to 25-hydroxyvitamin D ([25-OHD]) (DeLuca, 2004). This form is known as calcidiol. Approximately about 40 to 50% of circulating 25-OHD is derived from skin conversion (DeLuca, 2004). A second hydroxylation step occurs in the kidneys by 25(OH)D-1α-OHase to form the biologically active form of vitamin D 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$).[19] This active form is known as calcitriol.

Calcitriol interacts with its vitamin D nuclear receptor, which is present in the small intestine, kidneys, and other tissues.[19] It is primarily responsible for calcium absorption from the gut and enables normal bone mineralization and growth.[20] When calcitriol interacts with its vitamin D receptor in the osteoblast, the expression of the receptor activated nuclear factor κβ ligand is stimulated. When this occurs, immature monocytes are induced to become mature osteoclasts which dissolve the matrix and mobilize calcium and other minerals from the skeleton. To compensate for loss of calcium from the skeleton, calcitriol stimulates calcium reabsorption from the glomerular filtrate in the kidneys.[6,21]

Vitamin D sufficiency enhances calcium and phosphorus absorption by 30 to 40% and 80%, respectively.[6] Without adequate vitamin D, only 10 to 15% of dietary calcium and approximately 60% of phosphorus are absorbed.[6]

Aside from skeletal health, vitamin D modulates immunity, cell growth, and inflammation. It also is involved in processes that affect cell proliferation, differentiation,

and death.[6] Due to the lipid solubility of vitamin D, it can be sequestered in adipose tissue.[5] Obesity is associated with a lower vitamin D status. Individuals who are obese were found to have 20% lower vitamin D status after accounting for exposure to UVB and diet.[22]

2.1.8. Calcium and vitamin D metabolism during pregnancy

Maternal calcium absorption significantly increases during the second and third trimesters.[23] Calcium absorption during pregnancy is due to changes in maternal calcitropic hormones. For example, parathyroid hormone (PTH) and parathyroid hormone receptor proteins (PTHRP) are increased in the third trimester. PTHRP has PTH-like effects because they are recognized by PTH receptors. The purpose is to stimulate placental calcium transport to the fetus.[24] PTHRP also increases both calcium absorption in the small intestine and tubular resorption in the kidneys.[24] Along with PTH and PTHRP, both the active $1,25(OH)_2D_3$ and inactive 25-(OH)D forms of vitamin D affect calcium. In other words, maternal vitamin D metabolism is altered to enable transfer of calcium across the placenta to the fetal skeleton.

During pregnancy, the fetus is entirely dependent on the mother for vitamin D.[15] Serum [25-OHD] concentrations do not change during pregnancy, but an increase in 1-α-hydroxylase and additional synthesis in the placenta allows for an increase in the conversion of 25-OHD to $1,25(OH)_2D_3$.[1] The [25-OHD] passes from the placenta into the bloodstream of the fetus and fluctuates little during trimesters.[24] During the first and second trimesters, the fetus is developing most of its organ systems and is forming the collagen matrix. Calcitriol gradually increases at this time owing to increases in VDBP concentrations in maternal circulation. During the third trimester, calcification of fetal

skeleton begins via the increased production of calcitriol by the maternal kidneys and placenta.[1] It is estimated that maternal serum $1,25(OH)_2D_3$ levels double in order to increase the intestinal absorption of calcium.[25,26]

It is estimated that fetal calcium deposition peaks at 350 mg/day in the third trimester.[27] Therefore, women with low calcium intakes in late pregnancy (< 500 mg/day) are at greater risk of bone loss due to excessive bone resorption.[1] There is a greater capacity to absorb calcium; however, if the mother does not consume adequate amounts of dietary calcium she may be at risk for gestational complications.

2.1.9. Groups at risk for inadequate calcium intake

2.1.9.1. Individuals with lactose intolerance or cow's milk allergy

Lactose is a naturally occurring disaccharide present in milk. Lactose intolerance refers to symptoms of bloating, flatulence, and diarrhea that are produced due to low intestinal concentrations of the enzyme lactase to hydrolyze lactose into the monosaccharides glucose and galactose.[28] Primary lactase deficiency develops over time and begins typically after age two when the body begins to produce less lactase.[29]

Approximately 70% of the world's population has primary lactase deficiency.[29] In populations with a predominance in dairy foods in the diet, as few as 2% of the population has primary lactase deficiency, while the prevalence is 50 to 80% in Hispanic people, 60 to 80% in Black and Ashkenazi Jewish people and almost 100% in Asian and American Indian people.[29] Lactose malabsorption prevalence ranges from 53 to 100% in First Nations and Inuit adults.[30]

Inadequate intakes of calcium are frequently observed in the diets of individuals with lactose intolerance. This is thought to be due to the avoidance of milk products.

Cow's milk allergy is less common than lactose intolerance, affecting 0.6% to 0.9% of the population.[31] People with this condition are unable to consume any products containing cow's milk proteins and are therefore at higher risk of obtaining insufficient calcium.

2.1.9.2. Dietary factors

Vegetarians might be at a higher risk for low calcium intake because they may absorb less calcium than omnivores due to a higher consumption of plant foods containing oxalic and phytic acids.[5] Lacto-ovo vegetarians and non-vegetarians have similar calcium intakes.[32,33] However, vegans and ovo-vegetarians may not obtain sufficient calcium because of their avoidance of dairy foods.[32,33]

2.1.10. Consequences of maternal calcium deficiency during pregnancy

2.1.10.1. Gestational hypertension and preeclampsia

Preeclampsia is a major cause of death in pregnant women and newborn babies worldwide.[34] Gestational hypertension (HTN) is defined as systolic blood pressure greater than 140 millimeters of mercury (mm Hg) and/or diastolic blood pressure of greater than 90 mm Hg that has occurred on at least two occasions at least 4 hours to 1 week apart.[35] Gestational HTN occurs in approximately 5% of all pregnancies and 11% of all first pregnancies.[36] Preterm birth (birth before 37 weeks) can occur as a consequence of gestational HTN. Preeclampsia is an urgent medical condition that is categorized by having both gestational HTN and significant amounts of urinary protein.[1]

Inadequate calcium intakes during pregnancy can lead to the development of gestational HTN and preeclampsia due to the following reasons: a) release of PTH, thus increasing intracellular calcium and smooth muscle contractibility, and/or b) release of

renin from the kidney, leading to vasoconstriction and retention of sodium and fluid. The association between calcium intake and gestational blood pressure was determined through a trial conducted by the World Health Organization (WHO).[35]

The WHO conducted a calcium supplementation trial (1,500 mg/day or placebo) during pregnancy for women who usually consumed less than 600 mg calcium per day.[35] Calcium supplementation was associated with a small reduction in preeclampsia (4.1% versus [vs] 4.5%) that was shown by 35 weeks of gestation (1.2% vs 2.8%; $P = 0.04$). Preeclampsia (relative risk [RR] 0.68; 95% confidence interval [CI], 0.48-0.97) and severe gestational HTN (RR 0.71; 95% CI, 0.61-0.82) were significantly lower in the calcium group. Overall, there was a reduction in the severe preeclamptic complications index (RR 0.76; 95% CI, 0.66-0.89; life-table analysis, log rank test; $P = 0.04$). The severe maternal morbidity and mortality index was also reduced in the supplementation group (RR, 0.80; 95% CI, 0.70-0.91).

Similarly, a Cochrane review found that the average risk of preeclampsia was reduced in pregnant women (number [n] = 15,730) receiving calcium supplementation (RR 0.45).[37] The greatest effect occurred in women with low calcium intakes (mean intake < 900 mg/day) (RR 0.36). It's possible that women with low calcium intakes could reduce their risk of preeclampsia by 31 to 65% if they consumed an additional 1,000 mg of calcium daily. There were no statistical differences in women with an adequate dietary intake of calcium (mean intake of greater than or equal to 900 mg/day). However, the point estimate for this subgroup of women was a 38% reduction.

2.1.10.2. Preterm delivery

In the above mentioned WHO trial, preterm delivery and early preterm delivery were reduced among women who were younger than 20 years of age (RR 0.82; 95% CI, 0.67-1.01; RR 0.64; 95% CI, 0.42-0.98, respectively).[35] The neonatal mortality rate was lower (RR 0.70; 95% CI, 0.56-0.88) in the calcium group.

The Cochrane review found that women who chronically consumed inadequate calcium (< 900 mg/day) but were supplemented with 1,000 mg/day had a 24% reduced risk of preterm birth.[37]

2.1.10.3. Short-term maternal bone loss

Calcium supplementation equal to or greater than 1,000 mg/day during pregnancy has been shown to reduce bone turnover markers in late pregnancy.[38,39]

2.1.11. Risk factors for vitamin D deficiency in pregnant women

2.1.11.1. Latitude and limited sun exposure

The major cause of vitamin D deficiency is inadequate exposure to sunlight.[40] As mentioned earlier, many pregnant women in Manitoba are at risk due to reduced UVB exposure. Season, time of day, length of day, cloud cover, and smog, are among the factors that affect UV radiation exposure and vitamin D synthesis.[5] Cold climate, protective clothing and limited time spent outside often results in limited endogenous vitamin D production. Also, women who choose to wear long robes and head coverings for religious reasons are also at risk.[7]

2.1.11.2. Dark skin pigmentation

Melanin is responsible for the degree of skin pigmentation and protects the body from harmful ultraviolet radiation.[41] Melanin can reduce the photosynthesis of vitamin D

by approximately 50-fold.[42] Individuals with dark skin tone require at least three to five times longer exposure to make the same amount of vitamin D as a person with a white skin tone.[43,44] Therefore, individuals with darker skin are at higher risk for vitamin D deficiency.[42] Having a darker skin colour is a limiting factor for many people in Canada. Aboriginal women appear to have a higher prevalence of vitamin D deficiency.[45]

2.1.11.3. Obesity

Obesity, classified as a body mass index (BMI) value ≥ 30, is associated with lower serum [25-OHD] compared with normal weight individuals.[5] Obesity does not affect the skin's capacity to synthesize vitamin D, but greater amounts of subcutaneous fat sequester more of the vitamin and alter its release into the circulation.[5]

2.1.11.4. Dietary factors

Diets deficient in vitamin D are associated with milk allergy, lactose intolerance, ovo-vegetarianism, and veganism.[5] This is thought to be due to the limited consumption or avoidance of vitamin D rich foods.

2.1.12. Age and vitamin D status

Zhao and colleagues (2012) examined the factors associated with vitamin D inadequacy (defined as [25-OHD] = 30-50 nmol/L) and deficiency (defined as [25-OHD] < 30 nmol/L) among 1,814 women of childbearing age in the United States.[46] The age-adjusted prevalence of vitamin D inadequacy was 25.7% (95% CI, 22.3-29.5%), and 11.1% (95% CI, 8.8-14.0%) for vitamin D deficiency. Race/ethnicity other than non-Hispanic white and obesity were associated with increased risks, whereas dietary supplement use, milk consumption of ≥ 1 time/day, and potential sunlight exposure during May to October were associated with decreased risks for both vitamin D

inadequacy and deficiency ($P < 0.05$). Current smoking and having histories of diabetes and cardiovascular disease were also associated with an increased risk for vitamin D deficiency ($P < 0.05$). Age was not a significant risk factor.

However, a recent study determined that age is a risk factor. Campagna and colleagues (2013) determined the prevalence of vitamin D deficiency ([25-OHD] < 50 nmol/L) and severe deficiency ([25-OHD] < 25 nmol/L) in a Minnesota immigrant and refugee population (n = 1378).[47] Covariate data included country of origin, sex, age, month of test, and BMI. Vitamin D deficiency was significantly more prevalent in the Minnesota clinic immigrant and refugee population than among US-born patients (827 of 1378 [60.0%] vs 53 of 151 [35.1%]; $P < 0.001$). Severe vitamin D deficiency was also significantly more prevalent (208 of 1378 [15.1%] vs 12 of 151 [7.9%]; $P = 0.02$). Prevalence of vitamin D deficiency varied according to country of origin (42 of 128 Russian patients [32.8%] vs 126 of 155 Ethiopian patients [81.3%]; $P < 0.001$). The prevalence of vitamin D deficiency was greater when BMI was ≥ 25 (488 of 781 [62.5%] vs when BMI was < 25 (292 of 520 [56.2%]; $P = 0.02$). Vitamin D deficiency was present in 154 of 220 individuals (70.0%) 16 to 29 years old vs 123 of 290 (42.4%) in those older than 66 years ($P < 0.001$). Based on these results, age can present as a risk factor for vitamin D deficiency.

2.2. Diabetes in pregnancy

2.2.1. Insulin resistance

Insulin resistance is defined as a reduced tissue response to the effects of insulin on glucose metabolism. Such effects include reduced glucose uptake in muscle and fat

tissues, reduced liver glycogen formation, and accelerated liver glucose production.[48] Insulin resistance typically occurs during the second trimester of pregnancy. The hormones human placental lactogen, cortisol and prolactin all increase, causing insulin resistance. Along with insulin resistance from pregnancy, there is evidence that women with GDM have defects in pancreatic beta-cell function, and are unable to increase insulin secretion to compensate for the increased demand.[49,50] The inability to meet the demand for increased insulin secretion during pregnancy results in either impaired glucose tolerance (IGT) or GDM.[51]

2.2.2. Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus is defined as hyperglycemia with onset during pregnancy and is considered to be an early marker of glucose intolerance.[52] GDM is one of the most common complications of pregnancy, affecting 3.7% in the non-Aboriginal (multi-ethnic) population to 8 to 18% in the Aboriginal population in Canada.[53] The prevalence of GDM has increased in Manitoba over the last 20 years, with First Nations women having a 3-fold greater risk of developing GDM than in non-First Nations women.[54]

Untreated GDM can result in serious maternal and fetal adverse outcomes including maternal and perinatal morbidity. For the mother, outcomes can include preeclampsia, high Cesarean section (C-section) rate[55], and future type 2 diabetes mellitus (T2DM).[56] For the infant, outcomes can include macrosomia (hence, shoulder dystocia and newborn asphyxia), infant respiratory distress syndrome, and hypoglycemia.[55,57]

Insulin requirements during pregnancy significantly increase around 24 to 28 weeks of gestation. As such, screening for GDM is recommended to take place between 24 to 28 weeks of gestation.[52] However, screening can take place earlier if there is a suspected high risk for developing GDM. Risk factors for developing GDM include having a previous diagnosis of GDM, having prediabetes prior to pregnancy, having a high-risk ethnic background (Aboriginal, Hispanic, South Asian, Asian, African), being 35 years or older, having excessive weight gain during pregnancy or obesity prior to pregnancy (BMI of 30 or greater), having polycystic ovarian syndrome or acanthosis nigricans, corticosteroid use, history of giving birth to a large-for-gestational age baby ($\geq$ 9 lbs), or current fetal macrosomia or polyhydramnios.[52]

2.3. Vitamin D status and pregnancy

2.3.1. Low vitamin D status and GDM

Recent evidence has suggested that vitamin D is important for maintaining glucose homeostasis and insulin sensitivity in both human and animal models. Potential mechanisms relating to vitamin D, glucose homeostasis and insulin sensitivity include enhanced insulin synthesis and secretion[58], modulation of inflammatory processes that reduce functional capacity of beta-cells[59], stimulation of insulin receptors, and enhanced uptake of glucose into the muscle and adipose cells.[60] Thus, it can be hypothesized that maternal vitamin D deficiency during pregnancy can contribute to the development of insulin resistance, leading to IGT and GDM. Evidence from current studies suggests that maternal vitamin D deficiency is associated with an elevated risk for GDM.

Soheilykhah and colleagues (2010) compared serum [25-OHD] in Iranian

pregnant women with GDM (n = 54), IGT (n = 39), and normal glucose tolerance (n =

111).[61] Women were screened for GDM using a 50-g oral glucose tolerance test (OGTT).

Serum concentrations of [25-OHD] were obtained at 24 to 28 weeks of gestation, and

were classified into three groups (< 50 nmol/L as deficient, 50-72.5 nmol/L as

insufficient, and > 75 nmol/L as sufficient). The mean gestational age (GA) was 22.0 ±

8.5 weeks, and the mean maternal age was 27.4 ± 5.1 years. The authors found that

women with GDM had a 2.66-fold (95% CI, 1.26-5.6) increased risk of deficiency

compared with the normal glucose tolerance group.

A nested case-control study was conducted on a prospective cohort of 953

pregnant women to determine if there was an association between maternal [25-OHD] in

early pregnancy and the risk for GDM.[62] Vitamin D deficiency was defined as maternal

[25-OHD] < 50 nmol/L. Among the women, 57 women had developed GDM, and were

matched to 114 randomly selected women who were not diagnosed with GDM as

controls. Controls were matched to cases for the estimated season of conception (i.e. fall,

winter, spring, summer). The authors found that women who developed GDM had

significantly lower maternal plasma [25-OHD] at an average of 16 weeks of gestation

(60.5 nmol/L vs 75.3 nmol/L, $P < 0.001$). The difference remained significant after the

adjustment for maternal age, race, family history of diabetes, and pre-pregnancy BMI.

After adjustment for the above mentioned covariates, vitamin D deficiency was

associated with a 2.66-fold (odds ratio [OR] (95% CI): 2.66 (1.01-7.02)) increased risk

for GDM. Approximately 33% of women with GDM had serum [25-OHD] consistent

with vitamin D deficiency compared with only 14% of controls ($P < 0.001$). Maternal

plasma [25-OHD] were inversely associated with maternal adiposity as estimated by pre-pregnancy BMI ($r = -0.28$; $P = 0.04$ in GDM cases; $r = -0.025$; $P = 0.01$ in controls). Adjustment for season and physical activity did not change findings substantially.

Similarly, the results from a nested case-control study of 116 women with GDM and 219 controls also indicate that women with GDM had significantly lower [25-OHD] when compared with controls (56.3 vs 62.0 nmol/L, $P = 0.018$).[63] After adjusting for gestational age and maternal weight, serum [25-OHD] < 73.5 nmol/L was associated with a twofold greater likelihood of GDM (adjusted OR 2.21, 95% CI, 1.19-4.13).

Burris and colleagues (2012) also examined the association of second-trimester maternal plasma [25-OHD] during pregnancy with GDM.[64] Plasma [25-OHD] was measured at 26 to 28 weeks gestation, and was compared with the plasma glucose result from the 50-g OGTT in 1314 pregnant women. The authors found plasma [25-OHD] to be < 25 nmol/L in 4.0% of women with normal glucose tolerance, 5.7% of women with IGT, and 13.2% of women with GDM. After adjusting for sociodemographics, season, maternal BMI, gestational weight gain, and dietary factors, the results suggested that women with [25-OHD] of < 25 vs ≥ 25 nmol/L may have higher odds of GDM (OR 2.2; 95% CI 0.8-5.5). Also, the 1-hr glucose on the 50-g OGTT was inversely associated with [25-OHD] ($P < 0.01$).

Lastly, a 2012 meta-analysis examined seven observational studies which included a total of 2146 pregnant women, 433 of those with diagnosed GDM.[65] The authors defined vitamin D deficiency as serum [25-OHD] < 50 nmol/L. The results indicated that overall vitamin D deficiency was significantly related to the incidence of GDM with an OR of 1.61 (95% CI, 1.19-2.17; $P = 0.002$). Serum [25-OHD] was

significantly lower in women with GDM than in those with normal glucose tolerance (-5.33 nmol/L; 95% CI, -9.73 to -0.93; $P = 0.018$).

The above mentioned studies support the contention that deficient maternal [25-OHD] is associated with an increased risk of IGT and GDM. The results of these studies suggest that vitamin D influences glucose tolerance during pregnancy and provides support for additional studies of vitamin D as a potential intervention to prevent GDM or at least improve glucose tolerance. Also, since women with GDM are at higher risk for vitamin D deficiency, this may impact recommendations for screening for vitamin D deficiency.

2.3.2. Vitamin D status and infection in pregnancy

Research has confirmed that immune cells express vitamin D metabolizing enzymes.[66] Vitamin D has been increasingly recognized as an important modulator of bacterial infection. Therefore, it is thought that insufficient vitamin D may lead to impairment of the body's normal immune function.

Untreated chlamydial infection during pregnancy is associated with premature rupture of the membranes, preterm labour, low birth weight, and perinatal mortality.[67] Untreated gonococcal infection during pregnancy is associated with premature rupture of the membranes, premature birth, and low birth weight.[68] Untreated trichomoniasis during pregnancy is associated with premature rupture of the membranes, preterm birth, and low birth weight.[69] There have been no published studies regarding maternal vitamin D status in women with these infections.

Bacterial vaginosis (BV) infection is strongly associated with preterm birth.[70] Recently, it has been found that maternal vitamin D deficiency during pregnancy ([25-

OHD] < 37.5 nmol/L) is associated with a significantly higher risk of BV (adjusted OR 4.4, $P = 0.02$).[71]

Group B streptococcus (GBS) infection is the leading cause of neonatal sepsis and meningitis in developed countries.[72] One study of 2246 mother-child couples found a negative association between GBS vaginal carriage and level of vitamin D in umbilical cord blood ($P < 0.01$).[73]

These infections are serious conditions because they are associated with adverse pregnancy and fetal outcomes. Furthermore, pregnant women with GDM are already at an increased risk for negative maternal and fetal outcomes.

2.3.3. Birth outcomes

The induction of labour (IOL) is indicated when continuing the pregnancy places significant risks to the mother, the baby, or both. IOL will be of high priority for the following reasons: preeclampsia ≥ 37 weeks gestation, suspected fetal compromise or preterm premature rupture of the membranes. Other reasons include diabetes mellitus (blood glucose control may determine urgency), gestational hypertension ≥ 38 weeks, postdates (> 41 weeks) or post-term (> 42 weeks) pregnancy.[74] An elective IOL may be chosen if a medical indication cannot be identified.

Infant delivery by C-sections are usually carried out when risks to mother or infant are not amenable to normal vaginal delivery. C-sections may also be performed due to mechanical limitations. Emergency C-sections are performed when there are immediate health threats to the mother or fetus. The most common indications for delivery by C-section include previous delivery by C-section, breech presentation,

dystocia, and fetal distress.[75] However, some women may choose to have an elective C-section, whereby there are no indications of compromise to the mother or fetus.[76]

Preterm infant delivery (birth before 37 weeks) is the leading cause of neonatal mortality in the United States. Preterm labor precedes almost half of preterm births.[77] Spontaneous preterm labour occurs more frequently in pregnancies with diabetes. This can be related to an increased risk of intrauterine or perinatal asphyxia.[78] Other risk factors of preterm labour include previous preterm birth, periodontal disease, and low maternal BMI.[79]

Maternal obesity is associated with an increased risk of hypertensive disorders of pregnancy and difficulty delivering the infant via vaginal birth requiring C-section.[80]

Smoking during pregnancy is associated impaired fetal growth, preterm birth, and low birth weight.[81] Fetal exposure to illicit drugs, alcohol, and anemia are more likely to result in low birth weight ($< 2,500$ g).[82]

The newborn's overall well-being is assessed using the Apgar test.[83] Tests are completed at one minute and five minutes from the time of birth. Heart rate, respiratory effort, colour, muscle tone, and responsiveness to stimuli are scored with 0-2 points to give a total score of 0-10 for a newborn. At the 1-minute Apgar test, scores of 7-10 indicate that the baby will need only routine post-delivery care. Scores of 4-6 indicate that some assistance for breathing might be required. Scores under 4 can indicate lifesaving measures are needed. At the 5-minute Apgar test, a score of 7-10 is normal. If the score is under 7, the baby will continue to be monitored and retested every 5 minutes for up to 20 minutes.

2.3.4. Maternal vitamin D deficiency in pregnancy and lactation

A high prevalence of vitamin D deficiency exists among pregnant and lactating women. Vitamin D deficiency is well documented among Canadian women. For example, a study performed by Lebrun and colleagues (1993) sought to determine the prevalence of vitamin D deficiency among 80 mother-infant pairs in a native Cree community in Manitoba with a high incidence of rickets.[84] The majority of mothers (76%) and infants (43%) were found to be severely deficient in vitamin D, even in midsummer. The mean [25-OHD] was 26.2 nmol/L for the children and 19.8 nmol/L for the mothers. The authors attribute low vitamin D in this population to lack of fortified dairy products and vitamin D supplements.

There are data regarding vitamin D status of pregnant women located in Winnipeg. Weiler and colleagues (2005) obtained dietary information and serum [25-OHD] from 50 mother-infant pairs.[85] Vitamin D deficiency was defined at serum [25-OHD] < 37.5 nmol/L. There were 30 Caucasian and 20 non-Caucasian women (identified as First Nations, Asian, Black, Filipino or other). Approximately 75% of non-Caucasian and 30% of Caucasian pregnant women were vitamin D deficient, and only five (10%) had a [25-OHD] > 75 nmol/L. In total, 23 (46%) mothers and 18 (36%) of the infants had a plasma [25-OHD] consistent with deficiency. Also, most women (78%) reported taking multivitamin/mineral supplements during pregnancy, and 46% of these women had [25-OHD] in the deficient range. Almost all (93%) of the women without a deficiency had taken a supplement. Dietary intake from food sources was lower in the deficient women (149 vs 242 IU/day).

Similarly, the intakes of vitamin D and calcium were estimated in 121 pregnant Canadian women.[86] There were 33 Caucasian, 51 Inuit, and 37 Native Indian pregnant women, living in the Inuvik zone of the Northwest Territories. Plasma [25-OHD] and calcium were measured in mothers as well as in their infants at delivery. The daily mean vitamin D intake of Inuit and Indian women taking supplements was 324 ± 220 IU and without supplements was 163 ± 172 IU. This was significantly lower than in the Caucasian women taking and not taking supplements (528 ± 236 and 232 ± 172, respectively). Subsequently, there was a higher risk of vitamin D deficiency without supplementation in both Inuit and Native Indian (88.6% vs 48.4%) and Caucasian (63.5% vs 15.1%) mothers. At delivery, the plasma [25-OHD] was lower in Inuit and Native Indian mothers (50.1 ± 19.3 nmol/L) and their infants (34.2 ± 13.1 nmol/L) than Caucasian mothers (59.8 ± 29.4 nmol/L) and their infants (41.4 ± 23.5 nmol/L). The authors concluded that the vitamin D concentrations were low in this population due to lack of fortified dairy products and vitamin D supplements.

A cross-sectional analysis of [25-OHD] was conducted in pregnant women (n = 50), newborns via umbilical cord blood (n = 41) and children (n = 48) in Newfoundland and Labrador.[87] The prevalence of deficiency for the three groups studied revealed most women were in the deficient (< 25 nmol/L) or insufficient (25 to 75 nmol/L) ranges. For both winter and summer combined, the prevalence of insufficiency in pregnant women, newborns, and children was 78.0%, 82.4%, and 77.1%, respectively. In all three groups, there were significant differences studied between seasons, with the exception of maternal blood and female cord blood samples. Insufficiency was common in all groups for winter and summer, but more so in winter. The authors concluded that the

Newfoundland and Labrador population may be at increased risk for vitamin D insufficiency because of factors such as northern latitude and lifestyle.

A study performed in Southampton, United Kingdom reported maternal vitamin D status.[20] Among the 466 women who took part in the original study, the median serum [25-OHD] in late pregnancy was 50 nmol/L. Two hundred and thirty five women (50.4%) had [25-OHD] > 50 nmol/l, 132 women (28.3%) had concentrations between 27.5 and 50 nmol/l and 99 (21.2%) had concentrations < 27.5 nmol/L. Only three women had an intake of vitamin D that met the UK recommendation of 400 IU/day.

Some studies indicate that daily doses of 600 IU/day do not prevent deficiency in pregnant women.[15] For example, Lee and colleagues (2007) measured the plasma [25-OHD] in 40 mother-infant pairs, with the majority of women being Black (62.5%). The authors found that 76% of mothers and 81% of newborns had [25-OHD] < 50 nmol/L at time of birth despite mothers receiving approximately 600 IU/day of vitamin D from a prenatal multivitamin supplement and 2 cups of milk.[88]

Therefore, evidence indicates that the vitamin D status of the mother in pregnancy is a key determinant for the vitamin D status of her infant.

2.3.5. Vitamin D metabolism during infancy

Infants primarily depend on dietary vitamin D to meet their requirement from birth. Endogenous synthesis of vitamin D from sunlight can also be a source; however, the Canadian Dermatology Association states that infants younger than one year of age should avoid direct sunlight and also use sunscreen.[89]

Human milk typically contains a vitamin D concentration of 25 IU per liter or less.[90] An estimated 4,000 IU/day is required to maintain vitamin D sufficiency in both

mother as well as providing her infant with adequate vitamin D.[91] Thus, infants who are exclusively breastfed are prone to vitamin D deficiency, especially during the winter when neither they nor mothers can obtain vitamin D from sunlight. Infant vitamin D supplementation is usually available in droplet form. Each dose contains 400 IU of vitamin D_3.

2.3.6. Consequences of vitamin D deficiency in infants and children

Vitamin D deficiency results in abnormalities in calcium, phosphorus, and bone metabolism. There is a decrease in efficiency of intestinal dietary calcium and phosphorus absorption. As a consequence, PTH increases. Secondary hyperparathyroidism maintains serum calcium in normal range at the expense of mobilizing calcium from skeleton and increasing phosphorus wasting in kidneys. This results in a decrease of bone mineral density and muscle weakness.[15]

A severe vitamin D deficiency ($\leq$ 30 nmol/L) impairs mineralization of bone tissue (causing osteomalacia) and of growth plates (manifesting as rickets).[92] Vitamin D deficiency rickets is persistent in Canada despite guidelines for its prevention. In Canada, there were 40 children of First Nations ancestry who were treated for vitamin D deficiency rickets during 1972 to 1984.[93]

Recent evidence continues to show that rickets is a problem. For example, there have been 104 confirmed cases of rickets in Canada between 2002 and 2004. The overall annual incidence rate was 2.9 cases per 100,000. Ninety-two (88.5%) of the children had intermediate or darker skin. Ninety-eight (94.2%) had been breastfed, and three children (2.9%) had been fed standard infant formula. None of the breastfed infants had received vitamin D supplementation according to current guidelines (400 IU/day).[94] The majority

of children showed clinically important morbidity at diagnosis, including hypocalcemic

seizures (20 cases, 19.2%).[94] Other clinical manifestations during childhood include

fractures, lower-limb deformities, abnormal dentition or early childhood caries and

delayed developmental milestones.[20,95]

2.3.7. Risk factors for vitamin D deficiency in infancy

According to the Canadian Paediatric Society (2007) infants are at risk for

vitamin D deficiency if they are breastfed without vitamin D supplementation, have dark

skin pigmentation, or if the mother has vitamin D deficiency.[11] Therefore, infants'

vitamin D status is primarily dependent on maternal vitamin D status. Consequently, the

majority of infants in Winnipeg are at risk because the majority of pregnant women are

insufficient or deficient in vitamin D.

2.4. Clinical measurements for vitamin D

The metabolites of vitamin D include 25-hydroxyergocalciferol (25-OHD$_2$) and

25-hydroxycholecalciferol (25-OHD$_3$). [25-OHD] is the sum of these two forms and is

the best indicator of total vitamin D exposure.[5] It represents both the cutaneous

production of vitamin D and the oral ingestion of D$_2$ and D$_3$. Serum [25-OHD] is the

standard clinical measurement (biomarker) of vitamin D status (i.e. deficiency,

insufficiency, sufficiency, or intoxication).[5] The half-life of [25-OHD] is 2 to 3 weeks.

2.4.1. Screening for vitamin D deficiency

For the individual pregnant woman thought to be at increased risk of vitamin D

deficiency, the serum [25-OHD] can be used as an indicator of nutritional vitamin D

status.[96] According to the American College of Obstetricians and Gynecologists (2011),

there is insufficient evidence to screen all pregnant women for vitamin D deficiency, however, measuring serum [25-OHD] in pregnant women at increased risk of vitamin D deficiency can be considered.[96] Furthermore, it should be interpreted in the context of the individual clinical circumstance.

The Endocrine Society (2011) also advises screening for vitamin D deficiency in individuals at risk for deficiency. They recommend using the serum [25-OHD] to evaluate vitamin D status.[15] Cut-off values of [25-OHD] that indicate sufficiency, insufficiency, deficiency, and toxicity are debateable.

For persons living in Manitoba, recommendations for screening are provided by the Diagnostic Services of Manitoba.[97] A serious impediment was the backlog for serum [25-OHD] requests (there was a reported 18 month delay for results). As such, a guideline for risk stratification was released in 2012 whereby screening for vitamin D deficiency is indicated for specific reasons.[97] For example, individuals who are deemed at "high risk" for vitamin D insufficiency are those with recurrent fractures despite osteoporosis treatment, documented osteoporosis, or co-morbid conditions that affect vitamin D absorption or action. In which case, serum vitamin [25-OHD] is recommended to be measured "… following 3-6 months of an adequate supplement dose" (p. 3). The guideline indicates that 800 to 2,000 IU/day for an adult is "…adequate" (p. 3). Of note, there are no specific mentions for vitamin D intakes during pregnancy. However, there are recommendations for screening infants who are at high risk for vitamin D insufficiency ("If mothers have had minimal pre-natal vitamins, minimal summer sun exposure and minimal milk intake during the last trimester of pregnancy; consider testing

the infant and referring to a specialist for higher dose vitamin D supplementation if severely deficient" (p. 3)).

2.4.2. Assays

The quantification of [25-OHD] can be challenging due to its hydrophobic nature, its existence in several different molecular forms, and its tight binding to VDBP.[98] As a consequence, there is considerable variability among the assays and the laboratories that conduct the analyses.[5] Fortunately, a standard reference material for [25-OHD] became available in July 2009 that permits standardization of values across laboratories and may improve method-related variability.[5]

There are several methods for measuring [25-OHD]: radioimmunoassay, competitive binding protein assay, and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Radioimmunoassay uses antibodies that recognize both 25-OHD_3 and 25-OHD_2.[99] The coefficient of variability in the assay is 12 to 18% in the normal range of vitamin D (85 to 147.5 nmol/L) and 10 to 25% in the lower range of vitamin D (20 to 62.5 nmol/L).[100] The competitive binding protein assay measures the reagent that competes with vitamin D for its binding proteins.[99] This method often yields values about 30% higher but might not detect 25-OHD_2.[101]

LC-MS/MS is currently used as the reference method for quantitation of [25-OHD]. It has been shown to facilitate accurate separation and quantification of both 25-OHD_3 and 25-OHD_2, which comprise [25-OHD].[102] This method is performed by the Diagnostic Services of Manitoba located in the Health Sciences Centre hospital in Winnipeg.[97]

2.4.3. Functional definitions of optimal vitamin D status

Three systems are used interchangeably to measure vitamin D: Metric (ng/mL), International Units (IU) and Molar (nmol/L). One IU of vitamin D equals 25 ng (0.025 µg) or 65 pmol. Thus, 400 IU of vitamin D equals 10 µg or 26 nmol.[5]

Vitamin D status is primarily based on the amount of vitamin D required to achieve skeletal health. However, there is no consensus on the optimal [25-OHD] for skeletal health. The definition of vitamin status has been modified as a result of research into the relationship between vitamin D, PTH, serum calcium, and bone resorption. The following factors are considered:

1. The [25-OHD] level that maximally suppresses PTH secretion. The major stimulus for PTH secretion is a decrease in level of serum ionized calcium (e.g. inadequate calcium intake).[5] There is a plateau suppression of PTH when [25-OHD] is 75 nmol/L (Institute of Medicine, 2010). However, many individuals have very low [25-OHD] without increased PTH, thus 75 nmol/L does not guarantee PTH suppression. This represents an average value at a population level and does not account for wide variation in the [25-OHD] level.[103]

2. The [25-OHD] level that results in maximum intestinal absorption of calcium. The optimal calcium absorption occurs at [25-OHD] > 80 nmol/L.[104,105]

3. The [25-OHD] level at which there is no incremental increase in $1,25(OH)_2D_3$ level after administration of vitamin D, because the level of $1,25(OH)_2 D_3$ is adequate to meet demand.[106]

2.4.4 Classification of serum 25-hydroxyvitamin D ([25-OHD]) for population health

The Institute of Medicine (2010) supports that [25-OHD] at 50 nmol/L is required for skeletal health. This was the basis for developing the Dietary Reference Intake value for the Recommended Dietary Allowance (RDA). These recommendations were based on the assumption of minimal sun exposure due to public health concerns about skin cancer from ultraviolet radiation from the sun. The researchers concluded that [25-OHD] equal to 40 nmol/L covers the requirements of approximately half the population, [25-OHD] equal to 50 nmol/L covers the requirements of ≥ 97.5% of the population, and [25-OHD] >125 nmol/L should raise concerns about potential adverse effects (Table 2.1).[5]

The Canadian Paediatric Society (2007) defines deficiency at serum [25-OHD] < 25 nmol/L and sufficiency at serum [25-OHD] > 75 nmol/L (Table 2.2).[11] Osteoporosis Canada (2010) defines deficiency at serum [25-OHD] < 25 nmol/L and sufficiency at serum [25-OHD] > 75 nmol/L (Table 2.3).[12] The Endocrine Society (2011) defines deficiency at serum [25-OHD] < 50 nmol/L and sufficiency at serum [25-OHD] > 75 nmol/L (Table 2.4).[15]

Table 2.1 Classification of vitamin D status according to the Institute of Medicine (2010)

Health status	nmol/L
Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults	< 30
Generally considered inadequate for bone and overall health in healthy individuals	30-50
Generally considered adequate for bone and overall health in healthy individuals	≥ 50
Emerging evidence links potential adverse effects to high levels, particularly > 150 nmol/L	> 125

Table 2.2 Classification of vitamin D status according to the Canadian Paediatric Society (2007)

Health status	nmol/L
Deficient	< 25
Insufficient	25-75
Optimal	75-225
Pharmacological (potential adverse effects)	> 225
Potentially toxic	> 500

Table 2.3 Classification of vitamin D status according to the Osteoporosis Canada (2010)

Health status	nmol/L
Vitamin D deficiency	< 25
Vitamin D insufficiency	25-75
Desirable vitamin D status	> 75
Potential adverse effects	> 250

Table 2.4 Classification of vitamin D status according to the Endocrine Society (2011)

Health status	nmol/L
Deficiency	< 50
Insufficiency	52.5-72.5
Target	> 75
Potentially toxic	Not stated

2.4.5. Effect of supplemental vitamin D on serum [25-OHD]: General population

A systematic review of 167 published studies determined that for every 100 IU of vitamin D consumed daily the serum [25-OHD] increased by 1 to 2 nmol/L.[107] At 10,000

IU of vitamin D consumed daily, there is an expected increase in [25-OHD] of 100 to 200 nmol/L over time. Hypercalcemia or clinical hypercalciuria in absence of hypercalcemia requires vitamin D intakes greater than 40,000 IU/day. Hypercalcemia appeared in healthy adults only when serum [25-OHD] was greater than 750 nmol/L. Application of the Institute of Medicine's principle of the uncertainty factor resulted in the lowest observed adverse factor for serum [25-OHD] of 375 nmol/L.[108]

The absorption into the bloodstream of a bolus of oral cholecalciferol or ergocalciferol is complete within 72 hours.[109]

A meta-analysis of seven randomized trials evaluating serum [25-OHD] after supplementation found that cholecalciferol increased serum 25-OHD more effectively than ergocalciferol (mean difference 15.2 nmol/L) with the largest difference seen in weekly or monthly dosing.[100]

Both vitamin D_2 and D_3 effectively raise serum [25-OHD] levels.[107] It appears that nutritional doses of cholecalciferol and ergocalciferol are equivalent, but at high doses ergocalciferol is less potent. Cholecalciferol is estimated to be 1.7 to 3 times more potent than ergocalciferol based on the rise in serum [25-OHD] in adults.[7,111] Thus, if ergocalciferol is not consumed daily, it might not be effective in sustaining adequate status in the longer term.

2.4.6. Effect of supplemental vitamin D on serum [25-OHD]: Pregnancy

A prospective randomized study that included 180 total pregnant women (~27 weeks gestation) who were identified as either Indian Asian, Middle Eastern, African, Caucasian were randomized to receive either 800 IU D_2/day until delivery, 20,000 IU D_3 stat dose once, or no treatment.[112] The authors defined sufficiency at ≥ 50 nmol/L,

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insufficiency at 25 to 50 nmol/L, and deficiency at < 25 nmol/L for [25-OHD]. The supplemented groups had significantly higher [25-OHD] [daily dose (median) 42 nmol/L; stat dose (median) 34 nmol/l)] compared with the no treatment group [(median 27 nmol/L; $P < 0.0001$]. There were also significantly fewer women with secondary hyperparathyroidism in the supplemented groups (10% in daily dose vs 12% in stat dose vs 27% in the no treatment; $P < 0.05$). The cord [25-OHD] was significantly higher within the supplemented groups [daily dose median 26 (interquartile range [IQR] 17-45) nmol/l, stat dose median 25 (IQR 18-34) nmol/L vs median 17 (IQR 14-22) nmol/L in no treatment; $P = 0.001$]. Only a small percentage of women were vitamin D sufficient despite supplementation (daily dose 37% and stat dose 18% vs 15% in no treatment group). On the other hand, only 8% of babies were found to be vitamin D sufficient in mothers that were supplemented. Hence, the single stat dose or daily dose of vitamin D improved [25-OHD] significantly; however, the majority of women were still considered to be vitamin D insufficient.

A double-blind, randomized control trial (RCT) of 494 pregnant women who were identified as Black, Hispanic, or White at 12 to 16 weeks gestation were randomized to receive 400, 2,000, or 4,000 IU D_3/day throughout the duration of pregnancy.[113] Of the 494 women enrolled, 350 women continued until delivery. The target for [25-OHD] was 80 nmol/L or higher. There was a significant difference in the [25-OHD] at delivery and 1 month before delivery ($P < 0.0001$), and the percent who achieved sufficiency was significantly different by group. The greatest change was seen in the 4,000 IU group ($P < 0.0001$). The relative risk (RR) for achieving a concentration of 80 nmol/L or greater within one month of delivery was significantly different between

the 2,000 and the 400 IU groups (RR 1.52, 95% CI 1.24-1.86), the 4,000 IU and the 400

IU groups (RR 1.60, 95% CI 1.32-1.95) but not between the 4,000 IU and 2,000 IU

groups (RR 1.06, 95% CI 0.93-1.19). Circulating [25-OHD] had a direct influence on

circulating $1,25(OH)_2 D_3$ concentrations throughout pregnancy ($P < 0.0001$), with

maximal production of $1,25(OH)_2 D_3$ in the 4,000 IU group. There were no differences

between groups on any safety measure. There were no adverse events that were attributed

to vitamin D supplementation or circulating [25-OHD]. The authors concluded that

vitamin D supplementation of 4,000 IU/day for pregnant women is safe and most

effective in achieving sufficiency in all women and their neonates regardless of race,

whereas the current estimated average requirement (600 IU/day) is comparatively

ineffective at achieving adequate circulating [25-OHD] concentrations, especially in

African Americans.

A recent randomized trial examined the safety and efficacy of maternal and

neonatal supplementation using 2,000 IU and 4,000 IU D_3 in 257 pregnant women at 12

to 16 weeks gestation in two community health center networks in South Carolina.[114]

Participants were monitored for hypercalciuria, hypercalcemia, and [25-OHD]. Priori

caution limit for hypervitaminosis D was defined as urinary calcium:creatinine ratio ≥ 0.8

(measured monthly). Supplementation was to be discontinued if the urinary

calcium:creatinine ratio exceeded 1.0 or if the [25OHD] exceeded 250 nmol/L (measured

bimonthly). The results indicate that the maternal [25-OHD] increased from 56.7 nmol/L

at baseline to 90.4 nmol/L and 94.6 nmol/L in the 2,000 and 4,000 IU groups,

respectively. The monthly increase in maternal [25-OHD] differed between groups ($P <$

0.01). No supplementation-related adverse events occurred. Mean cord blood [25-OHD]

was 55.2 ± 25.7 nmol/L in 2,000 IU and 67.4 ± 33.2 nmol/L in 4,000 IU groups ($P = 0.024$). After controlling for ethnicity and study site, preterm birth and labor were inversely associated with pre-delivery and mean [25-OHD], but not baseline [25-OHD]. Therefore, it was shown that maternal supplementation with vitamin D at 2,000 and 4,000 IU/day during pregnancy improved maternal and neonatal vitamin D status.

2.4.7. Health risks and safety of supplemental vitamin D

The intake at which the dose of vitamin D becomes toxic is not clear. The first measurable consequences of vitamin D toxicity are hypercalciuria and hypercalcemia, which have been observed only at [25-OHD] above 220 nmol/L.[115] Plasma [25-OHD] above 225 nmol/L may be associated with hypercalcemia, and calcium deposition in tissues while levels above 500 nmol/L are considered toxic.[116]

Vitamin D toxicity can also cause non-specific symptoms such as anorexia, weight loss, polyuria, and heart arrhythmias. Vascular and tissue calcification can occur due to increased blood calcium levels, resulting in damage to the blood vessels, heart, and kidneys.[5]

Most studies specify a maximum safe daily dose of 10,000 to 40,000 IU and serum [25-OHD] of 500 to 600 nmol/L.[5] Symptoms of toxicity are unlikely to occur at intakes below 10,000 IU/day.[5]

A few studies investigating large doses of vitamin D in pregnancy provide evidence that doses above the recommended Institute of Medicine's upper limit of 4,000 IU/day are safe. For example, a dose of 10,000 IU/day for five months in pregnancy did not elevate levels into toxic range (> 225 nmol/L).[91]

It is important to acknowledge that urinary calcium excretion increases during pregnancy due to increases glomerular filtration rate.[117] Thus, the urinary calcium:creatinine ratio can be used and is the most sensitive early indicator of hypervitaminosis D. A non-fasting urinary calcium/creatinine ratio of 0.8 mg/mg or 2.27 mmol/mmol or greater can be used to monitor for toxicity.[113]

A systematic review by the Institute of Medicine (2010) addressed the safe upper level of serum [25-OHD]. There were insufficient data to *definitively* determine a safe upper serum level. Serum [25-OHD] above 125 nmol/L was associated with an increase in fracture in patients treated with high dose vitamin D[118] and conflicting studies describe a potential increased risk for some cancers (e.g. pancreatic, prostate) and mortality with levels above 75 to 120 nmol/L. A 2013 review suggests that there should be a degree of caution about recommending high serum [25-OHD] for the entire population as there is a lack of evidence.[119]

2.5. Overview of family physicians

2.5.1. Role of family physicians in prenatal care

FPs are the backbone of the community health system and are trained to take care of most health care needs, including prenatal medical care.[120] The ultimate goal of prenatal care is to provide a healthy maternal and fetal pregnancy outcome. Typical prenatal care involves appropriate pregnancy planning, education, risk assessment, and clinical monitoring throughout each trimester of pregnancy. Basic nutrition and food safety education should be provided by the FP. Common nutrition themes include intake

of kilocalories, folic acid, iron, calcium, and vitamin D.[121] Additionally, FPs are expected to be able to identify women who are at risk for and to treat basic nutritional deficiencies.

FPs may refer their patients to specialists if required. It is common for pregnant women to be cared for obstetricians or midwives for prenatal care if not looked after by the FP. If GDM is diagnosed during pregnancy, women can be referred to an endocrinologist for the management of GDM in pregnancy.

FPs have the opportunity to practice within a group of other allied health members including registered nurses and registered dietitians (RDs). Some FPs practice independently. Results from the National Physician Survey indicate that Canadian FPs are providing nutrition counselling, as well as collaborating with RDs or nutritionists.[122] The 2007 results revealed that 52% of FPs collaborated with RDs or nutritionists and 42% offered nutrition counselling as part of their practices.

2.5.2. Nutrition-related knowledge and clinical practices among health professionals

Very limited information exists in the literature that addresses the knowledge and practice regarding calcium and vitamin D nutrition among physicians. Power and colleagues (1999) mailed 1000 questionnaires on calcium nutrition to practicing American obstetrician-gynecologists.[123] The questionnaire consisted of 29 questions. Forced-choice questions were primarily used to assess the knowledge of calcium metabolism and physicians' practices. The response rate was 42.1% after two months. The authors found that most (75.4%) respondents considered making dietary recommendations an important part of their practice. However, the responses to the knowledge questions regarding calcium metabolism were predominately "don't know". Given the position that FPs have in the care of pregnant women and their offspring, it is

imperative to gain insight into the current knowledge, attitudes, and clinical practices

regarding calcium and vitamin D.

2.6. Overview of the survey process

2.6.1. The survey process

The survey is a commonly used research design used in health services research

and the social sciences.[124] Surveys are information-collection methods that are used to

collect information about individuals. Such information could include the knowledge,

feelings, values, preferences, and behaviours of individuals completing the survey.[125]

Surveys usually take place in the form of a questionnaire or an interview. They can be

used as a research instrument, within clinical trials, or as part of epidemiological studies.

Information from questionnaires is obtained by asking questions (known as *items*).

2.6.1.1. Self-completion questionnaires

A common type of questionnaire includes those that are self-completed, meaning

that the participant completes it alone or with assistance.[125] Questionnaires can be

distributed through the mailing system or electronically via the internet. Postal surveys

can consist of a cover letter or invitation, the questionnaire to be completed, and a

subsequent mailing of the questionnaire to non-responders.[126] Completed questionnaires

can be returned via mail, e-mail, through an online program, or faxed confidentially.

Self-completion questionnaires offer advantages over other research methods.[127]

Such advantages include a general low cost for data collection, as well as potential

coverage for widely dispersed samples. Furthermore, they are easy to implement and

generally require fewer personnel to carry out the project.[126] Respondents can complete

the questionnaire when it suits them and there is less pressure for an immediate response.[128] Keeping the respondents identity anonymous may help to promote honesty in disclosing answers.[128] Since an interviewer would not be involved during the completion of the questionnaire, this would eliminate the potential for interviewer bias.[128]

The main disadvantages include the potential for low response rates as well as the dependence on an accurate representative mailing list for the target sample.[126] They also require a level of literacy to complete the questionnaire.[129] There may be differences in literacy and education between the non-respondents and respondents, which may lead to bias.[129] A potential source of concern is that it is not possible to control who completes the questionnaire, or whether respondents have been assisted or influenced with their answers.[126] Despite these potential issues, this type of questionnaire can be beneficial.

Self-completion questionnaires are suited for simple topics and need to be easy to complete without assistance.[127] It is advised that the questionnaires should contain mostly closed-ended questions, and be shorter in length than interview-administered questionnaires.[130]

When developing a self-completion questionnaire, five main components need to be considered: a) the sample and survey design, b) format of the questionnaire, c) expert review and pilot test, d) data processing and analysis, and e) response rate. Each component will be described below.

2.6.1.1.1. Sample and survey design

The sample refers to the number and characteristics of the individuals completing the questionnaire. The design is how often the questionnaire takes place. A questionnaire

that is cross-sectional means that it takes place just once; longitudinal means that it takes place over time.[125]

During the initial steps of formulating a questionnaire, the population subgroup of interest as well as the research topic is determined. It is recommended to use a qualitative approach (such as semi-structured interviews and focus groups) to explore the research topic and identify key points for further study.[131] Along with the data from the literature review, the study objectives can be defined. The purpose of the questionnaire is to answer the study objectives.

2.6.1.1.2. Format of the questionnaire

Ideally, questionnaires that are valid and reliable should be used. However, existing questionnaires may not be available. Thus, developing or modifying a questionnaire will be required.

Questionnaire items may be open or closed-ended and be presented in various formats. As mentioned previously, questionnaire items that are to be self-completed are better suited for closed-ended questions.[130] Formats include those with statements with tick box categories, rating scales, visual analogue scales, symbols, and open-ended items.[125] Open-ended questions give respondents an opportunity to state a position in their own words.[125]

2.6.1.1.2.1. Closed-ended questions

A closed-ended question provides a choice of alternative answers from which the respondent is asked to select. Closed-ended questions can be attitudinal or factual, and the choice of answers or response options form part of the question (Oppenheim, 1992). For example, checklists, multiple choice questions, true/false questions, and attitude

scales are considered closed-ended.[133] A benefit to using closed-ended questions is that

they enable answers or responses to be compared among the respondents, require less

time to complete than open-ended questions, and are easy to code and process.[132]

Some uses and advantages of using statements with tick box categories ("yes",

"no", "don't know") include measurements of general attitude, are easily understood and

quick to complete, and generates data suitable for non-parametric statistical analysis.[134]

However, they cannot account for in-depth responses and can occasionally bias answers

by forcing respondents to consider options that they had not previously considered.[132]

2.6.1.1.2.2. Question wording and sequencing

How the questions are worded is critical to the design. Weaknesses in design and

wording can lead to biased reporting.[127] Two words that are often used inappropriately in

closed-ended questions are frequently and regularly. "Frequently" implies frequency

(hence, requires a frequency-based scale); "regularly" implies a pattern. Other words to

avoid include commonly, usually, many, some, and hardly ever.[135]

Questions should be filtered to exclude respondents lacking sufficient

information, a "don't know" category to reduce perceived threat, several questions on the

same topic to reduce guessing, avoidance of double-barrelled questions (e.g. "How

satisfied are you with the medications you are taking and the care you received from your

doctor?"), and general questions should precede specific ones.[136] Also, overly long

questions should be avoided as they are difficult to answer.[127] Questions that are leading

should also not be used (e.g. "Do you think patients should be examined by a doctor of

the same sex?").[127] Other wording practices to avoid include using shorthand (e.g.

abbreviations), negatively framing questions, using a passive voice, and words or phrases

with a strong point of view.[133] Complex words, technical terms, jargon, and phrases that are difficult to understand should also be avoided.[133]

2.6.1.1.2.3. Response dimensions

Response dimensions form the main element to the questions that are being asked.[133] For example, questions about events and behaviours could have the following response dimensions: the opportunity to experience or know something, occurrence of an event or behaviour within a set time period, and frequency (e.g. counts). Response dimensions for questions about attitudes and judgement include: degree of attractiveness (e.g. like/dislike, favour/oppose), satisfaction, intensity (e.g. a little, somewhat, or very much), certainty, and importance.

In order to avoid the expectation of particular answers, which is often the case for true/false questions, it is suggested to rephrase the question to include the response dimensions.[133] For example, begin the question by asking "How important is…..?', and then provide appropriate response categories, such as not at all, a little, somewhat, quite, extremely.

2.6.1.1.2.4. Reference period

The time frame for which the respondent is being asked to consider is known as the reference period.[133] Being explicit with the time period will reduce the assumption about how far back they should remember. Specific dates are preferred over "last week" or "last month". Also, the length of the reference time needs to be appropriate for the behaviour or event to be recalled by the respondent.

2.6.1.1.2.5. Response format

Response categories for a question need to be exhaustive and mutually exclusive so respondents can easily select only one response.[133] For questions that ask about one dimension (e.g. "How concerned….") five labeled categories are usually sufficient (not at all concerned, a little concerned, somewhat concerned, quite concerned, extremely concerned). When measuring the frequency of an event or behaviour the actual number of times the event or behaviour occurred during the reference period should be asked.[133] If the event in question is difficult to count or estimate, response categories may help respondents provide an answer.

2.6.1.1.2.6. Question order

The order of questions should begin with those that are easy to answer.[133] Also, items should be grouped that are similar in the topic; then, the items should be grouped within the topic that has similar response options. The questionnaire should end with personal and demographic questions.

2.6.1.1.3. Expert review and pilot test

2.6.1.1.3.1. Expert review

In order to produce a questionnaire that is usable and will provide the information that is needed, it is recommended to have an expert review it. Experts can include cognitive psychologists, survey methodologists, and professionals knowledgeable about research.

2.6.1.1.3.2. Pilot test

The final draft of the questionnaire should be pilot tested, preferably with a larger sample (often 30 to 100 individuals). However, the sample size will likely be dictated by

resources.[137] The sample should represent the variation in the types of respondent and respondent circumstances. During this stage, it is suggested to match the methods of administration to the intended distribution of the questionnaire. The aims of the pilot test are to look for how well questions work, estimate likely response rates, and to identify likely non-response bias.[137] A low or slow response rate can indicate that the questionnaire has problematic questions, whereby there could be potential misunderstandings of what a questions means or how it should be answered.[128]

2.6.1.1.4. Data processing and analysis

Analysis of the survey's data can be used to compute percentages, statistical evaluations, comparisons among groups, relationships among data, and changes over time.[125]

2.6.1.1.5. Response rate

Factors that have been shown to increase response rates include the use of incentives, the questionnaire has undergone piloting and testing, a questionnaire is clearly designed with a simple layout, participants are notified about the study in advance with a personalized invitation, a stamped addressed envelope is included in a postal questionnaire, respondents feel that they are stakeholders in the study, questions are phrased in a way that holds the respondent's attention, and a questionnaire has a clear focus and purpose as well as being concise.[134] It is best to avoid sending out questionnaires over the holiday season in order to encourage the best response rate. The response rate for family physicians varies; a 1999 study reported a response rate of 36.1% regarding a nutrition survey of Canadian physicians.[138]

2.7. Retrospective chart review

The retrospective chart review, also known as a medical record review, is a type of research design whereby pre-recorded, patient-centred data are used to address at least one research question.[139] Data may be the form of paper charts or electronically through patient software. In most cases, data are easily accessible to researchers, is less time consuming to collect compared with other study designs, and is less expensive. However, patient health records may have missing data, hence affecting their reliability and validity. Given the retrospective nature of this design, causation is difficult to support.[140]

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Chapter 3: Experimental Approach and Methodology

3.1. Overview

This project was conducted using a survey and a retrospective chart review.

3.1.1. Part 1: Survey

A questionnaire was completed by practicing FPs with the purpose of investigating the nutrition-related knowledge, opinions, clinical practices, and barriers that exist in providing calcium and vitamin D nutrition advice to pregnant patients. Quantitative data were analyzed using the statistical software program Statistical Package for Social Services (SPSS; version 14.0, Chicago, IL, USA). The results are presented in the Chapter 4.

3.1.1. Part 2: Retrospective chart review

Data were collected from the charts of 35 pregnant women with GDM attending a teaching hospital in Winnipeg, Manitoba between January 1, 2010 and December 31, 2013 and having at least one serum [25-OHD] measurement during their pregnancy. Maternal factors, measures of glycemia, birth outcomes, season of blood draw, dietary assessment, and use vitamin D supplements were determined from their charts. Quantitative data were analyzed using the statistical software program SPSS (version 23.0, Chicago, IL, USA). The results are presented in Chapter 5.

3.2. Research ethics approval

3.2.1. Part 1: Survey

The letter of consent and the questionnaire was approved by the University of Manitoba Joint Faculty Research Ethics Board (JFREB) on December 2013. The letter of

consent and questionnaire were modified based on feedback. The letter of consent and questionnaire were reapproved January 2014.

3.2.2. Part 2: Retrospective chart review

The retrospective chart review was approved by the University of Manitoba Health Research Ethics Board and the St. Boniface Hospital Research Review Committee in May 2014. The data collection sheets were revised twice and reapproved by both committees in May 2014 and February 2015.

3.3. Study population

3.3.1. Part 1: Survey

Practicing FPs in Manitoba who have a traditional family practice were eligible to complete the questionnaire. The random selection of FPs listed on the College of Physicians and Surgeons of Manitoba website is described in section 3.4.1.

3.3.1. Part 2: Retrospective chart review

Pregnant women presenting to the endocrine clinic at St. Boniface Hospital Winnipeg, Manitoba for GDM pregnancy and having at least one serum [25-OHD] measurement during their pregnancy care were eligible for the chart review. Additional inclusion and exclusion criteria are defined in Table 3.1. GA was calculated by the first day of their last menstrual period. GDM was diagnosed at the discretion of the endocrinologist.

Table 3.1 Inclusion and exclusion criteria for chart review

Inclusion Criteria	Exclusion Criteria
Diagnosed with GDM	Age < 18 years
Serum [25-OHD] result	Known calcium or parathyroid conditions
Resides in Manitoba	Ongoing disease: hepatic, renal, malignancy, metabolic bone disease

3.4. Study protocol

3.4.1. Part 1: Survey

A cross-sectional study design was used to carry out the survey. FPs were surveyed using a questionnaire. The survey consisted of a Letter of Consent (Appendix A) and questionnaire (Appendix B). The survey was developed by the principal investigator and the research supervisor. Respondents agreeing to participate in the study completed the questionnaire with questions that determined the knowledge, opinions, and clinical practices regarding prenatal calcium and vitamin D nutrition. It required 5-10 minutes to complete the questionnaire. Respondents completed the questionnaire independently and returned the questionnaire using a pre-paid return envelope. The questions asked addressed their knowledge, opinions, and clinical practices regarding calcium and vitamin D nutrition during pregnancy.

The questionnaire was composed of 31 closed-ended questions. Of these, seven questions addressed their knowledge, eleven questions addressed their clinical practice, and four addressed their opinions regarding prenatal calcium and vitamin D nutrition. One question was open-ended to encourage respondents to explain their thoughts toward prenatal calcium and vitamin D. There were four additional questions which asked if they recommend a prenatal multivitamin, refer to RDs, the frequency of referral to RDs, as

well as the importance of receiving prenatal nutrition education as continuing education. Lastly, five demographic questions were asked (area of practice, location of patients, prenatal patient load, number of years practicing family medicine, and gender).

The list of FPs was obtained from the College of Physicians and Surgeons of Manitoba website. The survey was proportionally mailed out to FPs in Winnipeg vs outside of Winnipeg (rural). As of February 3, 2014, there were an estimated 909 FPs across Manitoba who practice under "Family Practice". Of these, 485 FPs practiced in Winnipeg, and 424 practiced outside of Winnipeg. Therefore, approximately 53% of FPs practiced in Winnipeg, and 47% practice outside of Winnipeg. Hence, 265 surveys were mailed to FPs in Winnipeg, and 235 surveys were mailed outside of Winnipeg. Respondents were randomly selected using Microsoft Excel software program and the RANDBETWEEN function. Based on a previous nutrition survey study, the anticipated return rate of 36%, and the goal was to obtain a sample size of 180 respondents.[1]

Potential respondents were omitted if they had specialized practices indicated in their information from the College of Physicians and Surgeons of Manitoba. Examples of FPs who were omitted included those with the following practice information: Emergency Medicine, Critical Care, Palliative Care, Veterans Affairs, Nursing Home/Long-term Care, Geriatrics, Administrative, Workers Compensation, Cancer Care, Mature Women's Centre, Sport Medicine, St. Amant Centre, Department of Internal Medicine, Department of Community Medicine, Pan Am Clinic, or Addictions. FPs were also omitted if the mailing address was missing.

The survey was reviewed by an expert (an academic researcher in Family Medicine) in December 2013 and had undergone a pilot run to a group of five FPs in

January 2014. Based on the feedback, the letter of consent and questionnaire were modified and received approval by the University of Manitoba Joint Faculty Research Ethics Board in January 2014. An incentive (iPad) was suggested and respondents had the option of providing their email to enter the draw. The mail-out occurred in February 2014.

The identity of the responders was anonymous. A stamped addressed envelope was included for the return of completed questionnaires. We allowed for approximately two months for return of completed surveys. The entry form with the respondent's email address (if provided) was removed from each survey upon receipt of the survey. The draw for the iPad occurred at the end of May 2014. The answers to the knowledge-based questions were available on Dr. Carla Taylor's University of Manitoba website in May 2014.

3.4.2. Part 2: Retrospective chart review

A retrospective, cross-sectional chart review was used to obtain the serum [25-OHD] value and associated maternal and neonatal parameters of Manitoban women with GDM attending the St. Boniface Hospital endocrine clinic for diabetes care during pregnancy. The data collection sheets and master list for data collection were developed by the principal investigator and research advisor (Appendix C and D). Charts from January 2010 to December 2013 were used. Charts were included if: women were diagnosed with GDM, had at least one serum [25-OHD] result, and reside in Manitoba. Charts were excluded if: younger than 18 years, known calcium or parathyroid conditions, or ongoing disease (hepatic, renal, malignancy, metabolic bone disease) (Table 3.1). This is a convenience sample whereby the serum [25-OHD] were already

ordered based on the endocrinologist's discretion. The serum [25-OHD] were quantified by liquid chromatography tandem mass spectrometry at the Clinical Chemistry Lab at the Health Sciences Centre (Diagnostic Services of Manitoba). The charts were ordered using Health Records services at the St. Boniface Hospital.

The following maternal data were collected for each participant: age, gravidity, parity, height and weight (for BMI), GA at initial visit for those with GDM, location (to determine latitude), serum [25-OHD], season of blood draw for serum [25-OHD], 50-g and/or 75-g OGTT results, glycated hemoglobin (HbA1c), treatment strategy for GDM (diet or insulin treatment), and estimated intake of dietary and supplemental calcium and vitamin D from the dietary assessment note completed by the clinic's RD, and postpartum 75-g OGTT result for diagnosis of T2DM. Maternal GA was estimated at the time of blood collection for the OGTT and HbA1c, as well as for serum [25-OHD]. Other maternal outcomes included blood pressure at initial visit, incidence of hypertension (gestational or chronic) or preeclampsia, mode of infant delivery, and incidence of T2DM postpartum.

Neonatal data included GA at birth, infant birth weight, and Apgar scores at birth.

3.5. Statistical analyses

3.5.1. Part 1: Survey

Descriptive statistics (i.e. means, standard deviations, frequencies, and percentages) were computed for the measures obtained in the survey. Select questions were analyzed by sub-group to determine if factors including number of years practicing family medicine, gender, and location of practice (urban [Winnipeg] vs rural [outside of

Winnipeg]) influence knowledge, opinions, and clinical practices. Chi-square tests were used to determine whether there were differences in the responses between subgroups. Statistical significance between sub-groups was set using an alpha of 0.05 ($P < 0.05$). Statistical analyses were completed using SPSS (version 14.0, Chicago, IL, USA). The data were checked for accuracy by the principal investigator.

3.5.2. Part 2: Retrospective chart review

Analyses were computed using software SPSS (version 23.0, Chicago, IL, USA). Cut-off points for vitamin D concentrations were based on the Endocrine Society (2011) criteria for vitamin D categorization: deficient < 50 nmol/L, insufficient 50-74 nmol/L, and sufficient ≥ 75 nmol/L. Season of sample collection (Northern Hemisphere) was defined as fall (September to November), winter (December to February), spring (March to May), and summer (June to August).

Descriptive statistics were identified for participants' demographic and clinical characteristics as number and percentage of participants or mean ± standard deviation (SD) for normally distributed variables and median/interquartile range (IQR) for non-normally distributed variables. Shapiro-Wilk test was used to test for normality. Levene's test was used to determine homogeneity of variances. One-way analysis of variance was used to determine if there were significant differences in the means of serum [25-OHD] across trimesters and seasons. Pearson correlation analysis was used to investigate correlations between variables. Spearman's rank correlation coefficient and one-tailed Mann-Whitney U test were used for non-parametric data. For continuous variables, independent-sample Student's T test was used. Outliers (defined as mean ± 3 standard

deviations) were removed prior to statistical analyses. In all tests, the level of significance

was $P < 0.05$.

3.6. References

[1]Temple, N. J. (1999). Survey of nutrition knowledge of Canadian Physicians. *J Am Coll Nutr, 18*(1), 26-29.

Chapter 4: Calcium and Vitamin D in Pregnancy: A Survey of Family Physicians

4.1. Abstract

Background: It is unknown to what extent family physicians address calcium and vitamin D nutrition while providing prenatal care.

Objective: The purpose of this study was to investigate the nutrition-related knowledge and clinical practices of family physicians towards prenatal calcium and vitamin D.

Methods: Our survey on prenatal calcium and vitamin D nutrition consisted of 32 questions divided into four categories: demographics, knowledge, opinions, and clinical practices. We mailed this survey to 500 randomly selected family physicians working in Manitoba, Canada.

Results: The response rate was 22.2% (n = 111). Approximately one-third of family physicians are discussing calcium and vitamin D requirements and supplements with their prenatal patients. However, over half of respondents perceived receiving prenatal nutrition education as part of continuing medical education as very important or important. The top three perceived barriers to delivery of calcium and vitamin D advice were more urgent issues, lack of time, and forgetting to do so.

Conclusions: These results suggest that physicians would benefit from more training in nutrition. This survey indicates that multiple barriers exist that prevent family physicians from providing calcium and vitamin D advice.

4.2. Introduction

Part of prenatal medical care includes basic dietary advice and treatment of nutritional deficiencies[1]. Limited information exists about the knowledge and clinical practices of calcium nutrition among primary care providers[2]. Because adequate intakes of calcium and vitamin D are important for maternal and fetal health, we conducted a survey on calcium and vitamin D nutrition to determine the knowledge, opinions, and practices of FPs as well as what barriers exist for FPs to provide advice in an ambulatory care setting.

4.3. Methods

4.3.1. Participants

The addresses of physicians who practice under "family practice" were obtained from an electronic database. Surveys were proportionally mailed out to physicians in Winnipeg vs outside of Winnipeg. There were an estimated 909 physicians across Manitoba who practice under "family practice". Of these, 53% (485 physicians) practiced in Winnipeg, and 47% (424 physicians) practiced outside of Winnipeg. Hence, we mailed 265 surveys to those in Winnipeg, and 235 surveys outside of Winnipeg. Potential respondents were randomly selected through computer generated software. Based on a previous nutrition survey study[3], the anticipated return rate is 36%, with the goal to obtain a sample size of 180 respondents.

4.3.2. The survey

The survey received ethical approval by the University of Manitoba Joint Faculty Research Ethics Board. It was reviewed by an academic researcher in family medicine

and had undergone a pilot run to a group of five family physicians prior to being mailed out. The survey consisted of a Letter of Consent (Appendix A), questionnaire (Appendix B), and a stamped reply envelope. As an incentive, we offered the chance to win an iPad. The survey was mailed out in February 2014. We allowed a period of 8 weeks for return of completed surveys.

4.3.3. The instrument

The questionnaire consisted of 31 items (Appendix B). Responses to items were given either on a dichotomous scale with an additional "don't know" as a response, a 5-point Likert scale, or as free text. For identifying barriers they could check all answers that apply. We also requested demographic information (area of practice, location of patients, prenatal patient load, number of years practicing family medicine, and gender).

4.3.4. Statistical analysis

Data were analyzed using a personal computer-based software (SPSS version 14.0, Chicago, IL, USA. Frequencies were computed for the measures in the analyses. Differences in categorical variables (gender, years of practice [≤ 20 vs ≥ 21 years], location of practice [Winnipeg vs rural Manitoba]) were assessed using the $\chi2$ test and were tested for significance using an alpha of 0.05. Rural Manitoba was classified as any practicing family physician working outside of Winnipeg.

4.4. Results

Of the 500 surveys mailed out, 111 (22.2%) were returned. Results are presented for those who answered the questions. Demographic data and practice characteristics are displayed in Table 4.1. Respondents were split equally in representing both genders,

years of practice and location of practice, but the majority (78.0%) saw 1-10 prenatal patients per month (Table 4.1). Female physicians were significantly more likely than male physicians to provide care for 11 or more prenatal patients in a given month (35.8% vs 9.3%; χ2 = 12.26, P = 0.002).

Rural-based physicians were significantly more likely than Winnipeg-based physicians to care for 11 or more prenatal patients in a given month (33.3% vs 10.2%; χ2 = 9.45, P = 0.009).

When comparing physicians with fewer years of experience (≤ 20 years) to those with longer experience (≥ 21 years), physicians with less experience were more likely to work in a rural location (66.1% vs 37.7%; χ2 = 10.41, P = 0.005), provide prenatal care in a rural location (67.3% vs 39.2%; χ2 = 8.53, P = 0.004), and provide care for 11 or more prenatal patients in a given month (33.9% vs 9.6%; χ2 = 10.61, P = 0.005).

4.4.1. Calcium: Knowledge and opinions

Almost three out of four (73.9%) of physicians scored correctly on calcium dosage (500-600 mg) in over the counter (OTC) supplements, and 71.2% correctly identified that most Canadian women are not meeting current calcium recommendations.[5]

Many (72.5%) correctly identified the amount of calcium (300 mg) and vitamin D (100 IU) in 250 mL cow's milk.[6] Significantly more female than male physicians scored incorrectly for this item (20.4% vs 5.7%; χ2 = 6.28, P = 0.04).

Only 32.4% correctly identified the recommended daily amount of calcium (1000 mg)[7] and 64.9% correctly identified a higher risk for preeclampsia, preterm delivery, or excessive maternal bone loss with low calcium consumption (< 600 mg/day).[8] Almost one-quarter (24.1%) of respondents were "deterred" or "somewhat deterred" from

recommending calcium supplements due to a possible association with cardiac events in postmenopausal women.[9-11]

4.4.2. Calcium: Practices

About one in three (36.7%) respondents routinely discuss calcium requirements with their prenatal patients and 26.9% had suggested OTC calcium supplements within the last month. Years of practice influenced routine discussions about calcium requirements ($\chi2 = 4.38$, $P = 0.04$); physicians practicing for ≤ 20 years were significantly less likely to discuss calcium requirements when compared with those who have been practicing ≥ 21 years (26.8% vs 46.2%). Male physicians were more likely to suggest OTC calcium supplements to $> 75\%$ of patients vs female physicians (83.3% vs 13.3%; $\chi2 = 13.23$, $P = 0.001$).

4.4.3. Vitamin D: Knowledge and opinions

Given the choice of Manitoba's latitude, limited sun exposure, dark skin pigmentation, all of the above, or none of the above, concerning the risk factors that predispose pregnant women to vitamin D deficiency[12], 60.5% correctly identified all three risk factors.

Given the choice of 600 IU[7], 800-1,000 IU[13] or 1,500-2,000 IU[14], regarding the daily vitamin D recommendation that is appropriate for prenatal patients, just over half of physicians (55.5%) thought 800-1,000 IU/day is appropriate and 36.4% thought 1,500-2,000 IU/day is appropriate.

Physicians with more years of experience (≥ 21 years) were significantly more likely than physicians with less years of experience (≤ 20 years) to agree with the

Endocrine Society (2011) recommendation of 1,500-2,000 IU/day (46.3% vs 27.3%; χ2 = 4.25, $P = 0.04$).

Only 38.5% were "somewhat" concerned about vitamin D deficiency, and 56.1% neither agreed nor disagreed with the Diagnostic Services of Manitoba (2012) guidelines for screening for vitamin D deficiency.[15]

The majority (78.2%) did not know that low maternal vitamin D status (serum [25-OHD] < 75 nmol/L) is associated with a higher risk of gestational diabetes.[16]

4.4.4. Vitamin D: Practices

Similar to calcium, about one in three (38.2%) respondents routinely discuss vitamin D with their prenatal patients and 35.5% had suggested OTC vitamin D supplements within the last month. For those who recommended OTC vitamin D supplements, 1,000 IU/day was the most common dose by 53.8% of respondents followed by 2,000 IU/day by 35.9% of respondents. The majority (96.4%) of respondents had not ordered a serum [25-OHD] test for their prenatal patients within the last month.

4.4.5. Barriers

The top three barriers identified by respondents for providing calcium and/or vitamin D advice were "more urgent issues" (26.8%), "lack of time" (22.9%), and "forgetting to do so" (22.3%) (Table 4.2).

When comparing physicians with a less years of experience (≤ 20 years) with those with more years of experience (≥ 21 years), physicians with less years of experience were significantly more likely to select "unsure of what to recommend" as a barrier (22.7% vs 13.2%; χ2 = 4.65, $P = 0.03$).

4.4.6. Other important findings

Nearly all physicians indicated that they "always" recommend a folic acid containing prenatal vitamin (92.7%). A minority (16.4%) refer their pregnant patients to a RD for prenatal nutrition education, with "seldom" being the most common frequency at 47.1% followed by "about half the time" at 29.4%. A handful of respondents (4.5%) commented that their patients would be referred to an obstetrician who would then take over prenatal medical care. Receiving prenatal nutrition education as part of continuing professional development for physicians was perceived as "very important" (24.5%) or "important" (36.8%)

Table 4.1 Demographic and practice characteristics of respondents

Variable	Result *n* (%)
Gender (n = 109)	
Male	55 (50.5)
Female	54 (49.5)
Years of practice (n = 110)	
1-20	56 (50.9)
21 or more	54 (49.1)
Location of practice (n = 109)	
Winnipeg	51 (46.8)
Rural	57 (52.3)
Both Winnipeg and rural	1 (0.9)
Prenatal patients seen per month (n = 109)	
1-10	85 (78.0)
11 or more	24 (22.0)

Table 4.2 Perceived barriers to giving nutrition advice

Description	Result n (%)
More urgent issues	42 (26.8)
Lack of time	36 (22.9)
Forget to do so	35 (22.3)
Unsure of what to recommend	30 (19.1)
Don't feel confident giving nutrition advice	10 (6.4)
It's not part of my job	4 (2.5)

4.5. Discussion

FPs are primary care providers who also provide prenatal care[4]. Part of this care includes basic nutrition counselling and treatment of nutritional deficiencies including intake of kilocalories, folic acid, iron, calcium, and vitamin D[1]. FPs are the backbone of the community health care system, and it is essential to study their knowledge and opinions, behaviours, and concerns.

Our results show that a significant proportion of FPs early in their careers are working and providing prenatal care in rural areas. Since 2008, the number of physicians working in rural areas in Canada has increased five times faster than the rural population[17], which accurately reflects the high proportion of rural-based family physicians. Aside from a higher number of graduates working rurally, the number of female family physicians in the workforce continues to rise. Between 2009 and 2013, the number of female physicians increased by 22.5%, while the number of male physicians increased by 9.2%.[18] It would seem, then, that a higher proportion of newer graduating

physicians are female and tend to work in rural areas. Female physicians saw more pregnant women than male physicians, which may speak to a preference by pregnant women to be cared by female physicians.[19]

Our results indicate that there are gender and length of practice differences in knowledge, opinions, and practices regarding nutrition. Physicians with less years of experience (≤ 20 years) were less likely to discuss calcium nutrition and reported feeling "unsure of what to recommend" as a barrier. It would stand to reason that physicians gain knowledge and understanding of nutrition over time. Despite nutrition education as part of Canadian medical school curricula, a 2010 survey of medical students attending Canadian universities reported a significant number of students who were dissatisfied with the nutrition education they receive and their ability to provide relevant and appropriate nutrition counselling, especially for across the lifecycle and for chronic diseases.[20] Therefore, it seems that current, useful, practice-based nutrition education should be incorporated, not only into the medical school curriculum, but also regularly through continuing education (for example, annual conferences or webinars).

Since adequate intakes of calcium and vitamin D are important for maternal and fetal health[7], it is essential that pregnant women are educated on the importance of meeting their requirements. Approximately one-third of family physicians are discussing calcium and vitamin D requirements and supplements. For calcium, most physicians were aware of the low calcium intake among Canadian women, however, only one in three physicians correctly identified the recommended daily amount. An association of cardiac events and calcium supplementation in postmenopausal women appeared to influence the recommendation of calcium supplements. This may place pregnant women at risk for

poor calcium intake if alternatives to calcium supplements are not discussed (including

dairy and non-dairy sources of calcium). Male physicians were more likely to

recommend OTC calcium supplements to more patients, which may be due to a

difference in practice.[2] The recommended daily vitamin D requirement is not as clear.

[7,13,14] This may discourage family physicians from discussing vitamin D and

recommending supplements.

Vitamin D deficiency (defined as serum [25-OHD] < 50 nmol/L) is a common

health problem across the world,[21] and especially in Manitoba primarily due to our

latitude and limited sun exposure.[22] Most respondents are not screening for vitamin D

deficiency; this may have important health implications because treatment for deficiency

is probably less likely to occur.

It may be beneficial to consider the length of time allocated to prenatal medical

visits. Time constraints are a barrier for giving nutrition advice.[23,24] Since almost one-

quarter of physicians reported that "lack of time" was a barrier to discussing

calcium/vitamin D advice, perhaps reassessment of time allocation may be of benefit.

Given that "more urgent issues" was another significant barrier, perhaps proper prenatal

nutrition should be discussed at an additional appointment when urgent issues are not

being dealt with.

An interdisciplinary team approach to health care can help to improve access to

nutrition services. Integrating RDs into primary care can help to increase access to

nutrition care and complement family physicians' role in managing nutrition problems.[25]

Furthermore, they can provide nutrition education and develop practice-based tools

which may improve knowledge and clinical practice. Only a small proportion of family

physicians refer their patients to a dietitian for prenatal nutrition care. Awareness of nearby dietitians may help in coordinating prenatal nutrition care.

As with all self-administered surveys, this study was subject to a volunteer bias, which could be the reason for the low response rate. Physicians with an interest in nutrition were, perhaps, more likely to respond to the survey. Another point to consider is social desirability response bias, whereby respondents give socially acceptable responses rather than reporting their actual opinions or practices. Given these reasons, caution should be considered before generalizing these results beyond our study population of family physicians in Manitoba (Canada).

The responsibility of nutrition care may be unclear if both FP and obstetrician or midwife are involved in patient care. Further research into this area would be of benefit.

4.5.1. Clinical implications

We identified areas where nutrition knowledge may be improved. Daily amounts of calcium and vitamin D should be addressed at prenatal appointments. Prenatal nutrition education as part of professional development was perceived as important. Current, practice-based prenatal nutrition should be part of continuing medical education for physicians, first, because of its importance in maternal and fetal health during pregnancy, and, second, because nutrition is an ever-changing field.

4.6. Acknowledgements

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Chapter 5: Serum Vitamin D Concentrations and Glycemic Indices

in Women with Gestational Diabetes Mellitus

5.1. Abstract

Objective: To assess associations between maternal serum vitamin D concentration and glucose indices in a cohort of pregnant women with gestational diabetes mellitus (GDM).

Methods: Retrospective chart review of 35 women with GDM aged 19-38 years, treated at tertiary hospital in Manitoba, Canada (latitude 49-54°N).

Results: The mean serum [25-OHD] was 52.5 ± 24.1 nmol/L (range 14-109 nmol/L) obtained at 21.3 ± 7.4 weeks gestation. Over half of women (51.4%) were vitamin D deficient (defined as [25-OHD] < 50 nmol/L), and 28.6% of women were insufficient (defined as [25-OHD] 50-74 nmol/L). While age was correlated positively with serum [25-OHD] ($P < 0.05$), the 2-hr 75-g plasma glucose, maternal weight, and body mass index (BMI) inversely correlated with [25-OHD] ($P < 0.05$). Women with [25-OHD] < 50 nmol/L had higher 2-hr 75-g plasma glucose levels than women with [25-OHD] ≥ 50 nmol/L (8.8 ± 1.2 mmol/L vs 7.0 ± 1.7 mmol/L, $P = 0.015$). Women who reported taking a prenatal vitamin had significantly higher [25-OHD] concentrations (55.8 ± 23.5 nmol/L) compared with non-users (28.8 ± 17.4 nmol/L, P = 0.04).

Conclusion: Women with GDM have a high prevalence of vitamin D deficiency in our study. Associations between [25-OHD] and age, glucose tolerance, weight, and BMI were confirmed in this cohort. These correlations indicate that certain maternal factors may predispose pregnant women to vitamin D deficiency, which in turn suggests that vitamin D may influence glucose metabolism. Prenatal multivitamins containing vitamin D improved serum [25-OHD] concentrations, but higher doses may be required to achieve sufficient vitamin D levels.

5.2. Introduction

Vitamin D deficiency in pregnancy is common worldwide despite vitamin D fortification of some foods and some national dietary intake recommendations for deficiency prevention.[1] Limited exposure to UVB radiation strong enough to elicit endogenous synthesis and restricted intakes of food sources of vitamin D are likely contributors to vitamin D deficiency.[2] Neonatal hypocalcemic seizures and early childhood rickets are potential consequences to offspring born to mothers with severely deficient vitamin D concentrations.[3-5]

For improved bone health outcomes in infants and children, a maternal serum [25-OHD] $\geq$ 50 nmol/L is required[6], however, recent evidence suggests that concentrations of $\geq$ 75 mol/L or more may be needed for improving outcomes during pregnancy, including a reduced risk of GDM, preeclampsia, bacterial vaginosis, and small for GA infants.[7]

Pregnancy is an insulin resistant state, with sharp increases in insulin requirements in the second and third trimester. Women with GDM have defects in pancreatic beta-cell function, and are unable to increase insulin secretion to compensate for the increased demand.[8,9] Since vitamin D has been shown to play a role in maintaining glucose homeostasis and insulin sensitivity in both human and animal models[10-12], it is thought that vitamin D deficiency contributes to insulin resistance, leading to impaired glucose tolerance in pregnancy. For women with GDM, common short term risks to the mother include gestational hypertension and C-section[13], and macrosomia, birth trauma, and hypoglycemia for the neonate.[14,15] The defects in insulin secretion and action remain postpartum and increase the risk of T2DM in the mother.[16]

A number of studies have found that low maternal vitamin D status increases the risk of developing GDM.[17-20] A meta-analysis that included over 22,000 women found that the odds of developing GDM were 1.49 times higher for women with insufficient vitamin D levels (< 75 nmol/L) compared to those with sufficient vitamin D levels (> 75 nmol/L).[7]

In this study, we sought to assess that vitamin D status in a cohort of pregnant women with GDM in Manitoba, associations between serum [25-OHD] and glycemic indices, and to determine the impact of maternal factors on serum [25-OHD].

5.3. Materials and methods

5.3.1. Study population

Women presenting to a tertiary care hospital in Manitoba, Canada for GDM in pregnancy and having at least one serum [25-OHD] measurement during their pregnancy care were eligible for the chart review. Charts from January 2010 to December 2013 were used, and were excluded if younger than 18 years, known calcium or parathyroid conditions, or ongoing disease (hepatic, renal, malignancy, or metabolic bone disease). Thirty-five charts met the inclusion and exclusion criteria. This is a convenience sample whereby the serum [25-OHD] concentrations were already ordered based on the endocrinologist's discretion. Serum [25-OHD] concentrations were quantified by liquid chromatography tandem mass spectrometry at the Clinical Chemistry Lab at the Health Sciences Centre (Diagnostic Services of Manitoba). In 2010, the limit of detection was 15 nmol/L. One value below this limit of detection was assigned 14 nmol/L. Women with [25-OHD] < 50 nmol/L received cholecalciferol treatment. Data were recorded on a form

developed by the principal investigator (Appendix C) and a master list for data collection

(Appendix D). This study was approved by the University of Manitoba Health Research

Ethics Board (protocol #H2014:122) and the St. Boniface Hospital Research Review

Committee (protocol #RRC/2014/1392).

5.3.2. Diagnosis of GDM

GDM was diagnosed according to the Canadian Diabetes Association (CDA)

Clinical Practice Guidelines (CPG) (2008, 2013).[21,22] According to the 2008 CDA CPG,

diagnosis was based on the 50-g OGTT with a 1-hr post-load plasma glucose (PG) ≥ 10.3

mmol/L.[21] If women had 7.8-10.2 mmol/L, a subsequent 75-g OGTT was completed and

the threshold glucose values were fasting ≥ 5.3 mmol/L, 1-hr post-load ≥ 10.6 mmol/L,

and 2-hr post-load ≥ 8.9 mmol/L.[21] According to the 2013 CDA CPG, diagnosis was

based on the 50-g OGTT, with a 1-hr post-load ≥ 11.1 mmol/L.[22] If women had 7.8-11.0

mmol/L, a subsequent 75-g OGTT was completed and the threshold glucose values were

fasting ≥ 5.1 mmol/L, 1-hr post-load ≥ 10.0 mmol/L, and 2-hr post-load ≥ 8.5 mmol/L.[22]

Seven women (20%) did not have OGTT information available. Most women with GDM

were seen by a nurse and dietitian and were taught home blood glucose monitoring.

5.3.3. Data collection

The following maternal data were collected: age, gravidity, parity, height and

weight at initial appointment (for BMI), smoking status, substance abuse, alcohol abuse,

incidence of anemia, infection (bacterial vaginosis and GBS) and gestational HTN, GA at

initial visit, location (to determine latitude), serum [25-OHD], season of blood draw and

GA for serum [25-OHD], 50-g and/or 75-g OGTT glucose results and HbA1c, treatment

strategy for GDM (diet or insulin treatment), estimated intakes of dietary and

supplemental vitamin D (Appendix C). Incidence of T2DM based on 75-g OGTT or

HbA1c in mothers postpartum was also obtained (range 5-178 weeks postpartum).

Diagnosis of T2DM was based on the endocrinologist's discretion according to the

Canadian Diabetes Association Clinical Practice Guidelines (2008, 2013).[21,22] Mode of

delivery, gestational age at birth, and birth weight were also obtained.

5.3.4. Data analysis

We performed statistical analyses using software (SPSS version 23.0, Chicago,

IL, USA). Cut-off points for vitamin D concentrations were based on the Endocrine

Society (2011) criteria for vitamin D categorization: deficient < 50 nmol/L, insufficient

50-74 nmol/L, and sufficient ≥ 75 nmol/L.[23] Season of sample collection (Northern

Hemisphere) was defined as fall (September to November), winter (December to

February), spring (March to May), and summer (June to August).

Descriptive statistics are presented for participants' demographic and clinical

characteristics as number and percentage of participants or mean ± standard deviation

(SD) for normally distributed variables and median/interquartile range (IQR) for non-

normally distributed variables. Normality was determined by the Shapiro-Wilk test.

Levene's test was used to determine homogeneity of variances. For continuous variables,

Student's T test was used. One-way analysis of variance was used to determine if there

were significant differences in the means of serum [25-OHD] across trimesters and

seasons. Pearson correlation analysis was used to investigate correlations between

variables. Spearman's rank correlation coefficient and one-tailed Mann-Whitney U test

were used for non-parametric data. Multiple linear regression was used to assess the

relationship between [25-OHD] and 2-hr glucose on the 75-g OGTT. Outliers were removed prior to statistical analyses. In all tests, the level of significance was $P < 0.05$.

5.4. Results

5.4.1. Maternal characteristics

The number of women with available results for each variable is shown in Table 5.1. In total, 35 women were eligible for the chart review. All women had singleton pregnancies. The median age was 28 years (range 19-38 years). Measured mean weight was 93.1 ± 17.3 kg at 20.1 ± 7.5 weeks gestation. The majority of women (82.9%) had a BMI classified as obese (BMI $\geq$ 30). Mean 2-hr 75-g plasma glucose and HbA1c was 8.1 ± 1.6 mmol/L and $5.8 \pm 0.5\%$, respectively. The women's gravidity ranged from one to nine with an average of 4.0 ± 2.0 pregnancies. Most women (77.1%) reported taking prenatal vitamins which contain approximately 400 IU/day vitamin D. Over half of women (65.7%) had estimated vitamin D intake of < 100 IU/day and only one woman reported taking a vitamin D supplement. Lactose intolerance was reported by 20.0% of women. The majority of women (80.0%) required insulin for GDM treatment. Of all women, 14 women (40.0%) reported nicotine use, one woman (2.9%) reported alcohol abuse, and 3 women (8.6%) reported substance abuse during pregnancy. Three women (8.6%) were anemic (defined as hemoglobin $\leq$ 100 g/L) during pregnancy. About a third of women tested positive for BV and GBS (28.6% and 34.3%, respectively). Eight women (22.9%) developed gestational HTN. A total of 24 women were tested for T2DM postpartum. Of these, eight women (33.3%) developed T2DM based on HbA1c or 75-g OGTT at a median 18 weeks postpartum.

Infants were delivered at mean GA of 38.0 ± 2.0 weeks, with a quarter (25.7%) of infants born preterm (prior to 37 weeks) (Table 5.2). Mean infant birth weight was 3489 ± 648 g. Of these infants, six were considered macrosomic (15.2%). A third of infants were delivered by C-section (33.3%).

5.4.2. Vitamin D status

Over half (51.4%) of our study population was vitamin D deficient ([25-OHD] < 50 nmol/L); 28.6% were vitamin D insufficient ([25-OHD] 50-74 nmol/L); and 20.0% were vitamin D sufficient based on serum [25-OHD] ≥ 75 nmol/L (Table 5.3). Of the vitamin D deficient women, 38.9% were classifiable as severely vitamin D deficient (< 30 nmol/L). The mean serum [25-OHD] was 52.5 ± 24.1 nmol/L (range 14-109 nmol/L) obtained at 21.3 ± 7.4 weeks gestation and a median latitude of 53.0 degrees N. Differences in serum [25-OHD] among the trimesters and seasons were not significant. Thirty-one percent of the blood draws occurred in the fall, 9% in the winter, 34% in the spring, and 36% in the summer. The mean serum [25-OHD] concentrations were highest in the fall and summer seasons (59.1 ± 7.9 and 55.8 ± 8. nmol/L, respectively), and lowest in the winter (24.7 ± 5.5 nmol/L) (Table 5.4).

Women who consumed < 100 IU of dietary vitamin D had significantly lower serum [25-OHD] compared to women who consumed > 100 IU vitamin D (46.0 ± 22.1 vs 64.6 ± 22.4 nmol/L, $P = 0.041$). Most women (77.1%) reported taking a prenatal multivitamin. Women who reported using prenatal multivitamins had significantly better serum [25-OHD] when compared to women who were not using prenatal multivitamins (55.8 ± 23.5 nmol/L vs 28.8 ± 17.4 nmol/L, $P = 0.036$). Women who reported lactose

intolerance had significantly lower serum [25-OHD] when compared to women who were lactose tolerant (36.1 ± 14.4 nmol/L vs 66.2 ± 26.4, $P = 0.028$).

Women who were obese (based on a BMI ≥ 30) had significantly lower serum [25-OHD] compared to women who were normal or overweight (based on BMI < 30) (47.2 ± 21.7 nmol/L vs 77.8 ± 19.6 nmol/L, $P = 0.03$).

5.4.3. Serum [25-OHD] and measures of glycemia

For glycemic outcomes, a statistically significant correlation was found between [25-OHD] and 2-hr glucose on the 75-g OGTT (r = -0.487, $P = 0.035$) (Figure 5.1), but not with the fasting blood glucose, 1-hr glucose or glycated hemoglobin (Table 5.5).

Women who were vitamin D deficient (< 50 nmol/L) tested significantly higher on the 2-hr 75-g OGTT than women who were vitamin D insufficient or adequate (≥ 50 nmol/L) (8.8 ± 1.2 vs 7.0 ± 1.7 mmol/L, $P = 0.039$). There was a trend for slightly higher HbA1c values in vitamin D deficient women ($5.9 \pm 0.5\%$ vs $5.6 \pm 0.4\%$, $P = 0.063$) (Table 5.6).

Table 5.7 displays correlations between glycemia indices and maternal factors. There was a trend for a positive correlation between maternal weight and 2-hr glucose on the 75-g OGTT (r = 0.429, $P = 0.067$). Maternal weight (r = 0.430, $P = 0.012$) and BMI (r = 0.521, $P = 0.002$) were strongly correlated with HbA1c.

5.4.4. Associations with [25-OHD]

Relationships of serum [25-OHD] with variables of interest are shown in Table 5.5. Serum [25-OHD] showed a significant positive correlation with age (r = 0.391, $P = 0.020$). On the other hand, serum [25-OHD] showed significant negative correlations with weight (r = -0.336, $P = 0.049$) and BMI (r = -0.378, $P = 0.025$).

Because there were too few participants in the vitamin D category of vitamin D

sufficient (≥ 75 mol/L) for meaningful statistical analyses, women categorized as either

vitamin D insufficient or adequate were combined into one category (≥ 50 nmol/L) for

subsequent statistical analysis (Table 5.6). Compared to women with [25-OHD] ≥ 50

nmol/L, women with [25-OHD] < 50 nmol/L were significantly more likely to be

younger ($P = 0.030$), weigh more ($P = 0.027$), and have a higher BMI ($P = 0.028$). There

were no significant associations with serum [25-OHD] when comparing women who

tested positive for BV or GBS infections with women who tested negative for these

infections. No significant associations with serum [25-OHD] were seen with women who

developed gestational hypertension or delivered via C-section. Latitude, height, gestation

at 50-g and 75-g OGTTs, 1-hr 50-g PG, gravidity, parity, gestational age at delivery,

infant birth weight, and diagnosis of T2DM postpartum were not significantly associated

with serum [25-OHD].

Table 5.1 Maternal and clinical characteristics of participants

Variable*	*n* (%)	Mean ± SD or median (IQR)†
Age		
Maternal age (years)†	35	28.0 (10.0)
Anthropometrics		
Weight (kg)	35	93.1 ± 17.3
Height (cm)	35	162.8 ± 6.7
BMI (kg/m^2)	35	35.1 ± 6.4
Gestation at weight (weeks)†	35	19.0 (16.0)
Glycemia indices		
Gestation at 50-g OGTT (weeks)†	25	13.0 (13.0)
1-hr 50-g OGTT PG (mmol/L)	25	10.6 ± 2.1
Gestation at 75-g OGTT (weeks)	19	17.8 ± 8.0
Fasting plasma glucose (mmol/L)	19	5.3 ± 1.0
1-hr 75-g OGTT PG (mmol/L)	18	12.0 ± 2.1
2-hr 75-g OGTT PG (mmol/L)	19	8.1 ± 1.6
Gestation at HbA1c (weeks)†	33	21.0 (15.0)
HbA1c (%)	33	5.8 ± 0.6
Serum [25-OHD]		
Serum [25-OHD] (nmol/L)	35	52.5 ± 24.1
Gestational at [25-OHD] (weeks)†	35	22.0 (14.0)
Latitude (degrees)†	35	53.0 (4.0)

Serum [25-OHD] (nmol/L) by trimester

1st trimester	6	65.8 ± 17.5
2nd trimester	19	46.1 ± 22.9
3rd trimester	10	56.5 ± 27.4

Serum [25-OHD] (nmol/L) by season

Fall	11	59.9 ± 7.9
Winter	3	24.7 ± 5.5
Spring	12	50.1 ± 6.0
Summer	9	55.8 ± 8.1

Dietary factors

Prenatal multivitamin in pregnancy

No	4 (11.4%)	-
Yes	27 (77.1%)	-
Unknown	4 (11.4%)	-

Estimated dietary vitamin D

< 100 IU	23 (65.7%)	-
100-200 IU	7 (20.0%)	-
201-300 IU	1 (2.9%)	-
> 300 IU	1 (2.9%)	-
Unknown	3 (8.6%)	-

Vitamin D supplement in pregnancy		
No	34 (97.1%)	-
Yes	1 (2.9%)	-
Reported lactose intolerance		
No	5 (14.3%)	-
Yes	7 (20.0%)	-
Unknown	23 (65.7%)	-
Pregnancy outcomes		
Required therapeutic insulin		
No	7 (20.0%)	-
Yes	28 (80.0%)	-
Gravidity	35	4.0 ± 2.0
Parity†	35	2.0 (2.0)
Nicotine use in pregnancy		
No	21 (60.0%)	-
Yes	14 (40.0%)	-
Alcohol abuse in pregnancy		
No	34 (97.1%)	-
Yes	1 (2.9%)	-
Substance abuse in pregnancy		
No	32 (91.4%)	-
Yes	3 (8.6%)	-

Anemia in pregnancy		
No	31 (88.6%)	-
Yes	3 (8.6%)	-
Unknown	1 (2.9%)	-
Bacterial vaginosis		
Negative	17 (48.6%)	-
Positive	10 (28.6%)	-
Unknown	8 (22.9%)	-
Group B streptococcus		
Negative	12 (28.6%)	-
Positive	10 (34.3%)	-
Unknown	13 (37.1%)	-
Hypertension		
Gestational	8 (22.9%)	-
Preexisting	1 (2.9%)	-
Diagnosis of T2DM postpartum		
No	16 (45.7%)	-
Yes	8 (22.9%)	-
Unknown	11 (31.4%)	-

†Median (interquartile range) for non-normally distributed variables.
*For those tested.

Table 5.2 Birth outcomes for infants born to participants

Variable*	n (%)	Mean ± SD or median (IQR)†
Gestational age at delivery (weeks)†	35	38.0 ± 2.0
Preterm birth (< 37 weeks)	9 (25.7%)	-
Infant birth weight (g)	33	3489 ± 648
Infant weight classification		
Low birth weight (< 2,500g)	3 (9.1%)	-
Normal weight (2,500-4,000-g)	24 (72.7%)	-
Macrosomia (4,000-4,500-g)	6 (15.2%)	-
Route of delivery		
C-section delivery	11 (33.3%)	-
Emergency C-section	7 (21.2%)	-
Elective C-section	4 (12.1%)	-

†Median (interquartile range) for non-normally distributed variables.
*For those tested.

Table 5.3 Prevalence of vitamin D deficiency

Serum [25-OHD] category	n	%
Deficiency (< 50 nmol/L)	18	51.4
Insufficiency (50-74 nmol/L)	10	28.6
Sufficiency (≥ 75 nmol/L)	7	20.0
Total	35	100.0

Table 5.4 Serum 25-hydroxyvitamin D and related parameters

Variable*	*n* (%)	Mean ± SD or median (IQR)†
Serum [25-OHD] (nmol/L)	35	52.5 ± 24.1
Gestational age at [25-OHD] (weeks)†	35	22.0 (14.0)
Latitude (degrees)†	35	53.0 (4.0)
Serum [25-OHD] by trimester (nmol/L)		
1ˢᵗ trimester	6	65.8 ± 17.5
2ⁿᵈ trimester	19	46.1 ± 22.9
3ʳᵈ trimester	10	56.5 ± 27.4
Season of blood draw for [25-OHD]		
Fall	11 (31.4%)	-
Winter	3 (8.6%)	-
Spring	12 (34.3%)	-
Summer	9 (25.7%)	-
Serum [25-OHD] by season (nmol/L)		
Fall	11	59.9 ± 7.9
Winter	3	24.7 ± 5.5
Spring	12	50.1 ± 6.0
Summer	9	55.8 ± 8.1

†Median (interquartile range) for non-normally distributed variables.
*For those tested.

Table 5.5 Relationships of serum 25-hydroxyvitamin D with variables of interest in bivariate analyses

Variable**	n	Correlation coefficient*	P
Maternal age (years)†	**35**	**0.391**	**0.020**
Latitude†	35	-0.258	0.134
Weight (kg)	**35**	**-0.336**	**0.049**
Height (cm)	35	0.093	0.597
BMI (kg/m^2)	**35**	**-0.378**	**0.025**
Gestation at [25-OHD] (weeks)†	35	-0.199	0.253
Gestation at 50-g OGTT (weeks)†	25	0.390	0.053
1-hr 50-g OGTT PG (mmol/L)	25	0.019	0.927
Gestation at 75-g OGTT (weeks)	19	0.217	0.371
Fasting PG (mmol/L)	19	-0.117	0.634
1-hr 75-g OGTT PG (mmol/L)	18	-0.020	0.939
2-hr 75-g OGTT PG (mmol/L)	**19**	**-0.487**	**0.035**
Gestation at HbA1c (weeks)†	33	-0.221	0.217
HbA1c (%)	33	-0.290	0.102
Gravidity	35	-0.030	0.862
Parity†	35	-0.252	0.144
Gestational age at delivery (weeks)	35	0.237	0.170
Infant birth weight (g)	33	0.045	0.802

*Pearson's correlation coefficient except where indicated by †.
†Spearman's correlation for non-normally distributed variables.
**For those tested.*

Table 5.6 Maternal and clinical characteristics of participants by vitamin D group

Variable*	[25-OHD] < 50 nmol/L (mean ± SD or median (IQR)†)	[25-OHD] ≥ 50 nmol/L (mean ± SD or median (IQR)†)	P
Number (n, %)	18 (51.4%)	17 (48.6%)	-
Serum [25-OHD] (nmol/L)	33.6 ± 12.2	72.4 ± 15.9	-
Maternal age (years)†	**26.0 (12.0)**	**30.0 (10.0)**	**0.015**
Latitude (degrees)†	53.0 (1.0)	53.0 (4.0)	0.153
Weight (kg)	**99.3 ± 15.8**	**86.6 ± 16.8**	**0.027**
Height (cm)	163.0 ± 6.6	162.6 ± 6.9	0.851
BMI (kg/m^2)	**37.4 ± 5.9**	**32.7 ± 6.1**	**0.028**
Gestation at 50-g OGTT (weeks)†	10.5 (6.0)	13.0 (16.0)	0.182
1-hr 50-g OGTT PG (mmol/L)	10.4 ± 2.3	10.8 ± 1.8	0.612
Gestation at 75-g OGTT (weeks)	16.1 ± 8.1	20.3 ± 7.7	0.276
Fasting PG (mmol/L)	5.3 ± 1.2	5.3 ± 0.9	0.929
1-hr 75-g OGTT PG (mmol/L)	12.3 ± 2.5	11.6 ± 1.3	0.542
2-hr 75-g OGTT PG (mmol/L)	**8.8 ± 1.2**	**7.0 ± 1.7**	**0.015**
Gestation at HbA1c (weeks)†	22.5 (12.0)	16.0 (17.0)	0.122
HbA1c (%)**	5.9 ± 0.5	5.6 ± 0.4	0.063
Gestational age at delivery (weeks)	37.4 ± 1.6	37.8 ± 1.7	0.573
Infant birth weight (g)	3581 ± 660	3378 ± 637	0.378
T2DM diagnosis postpartum (n, %)*	5 (62.5%)	3 (37.5%)	-
Lactose intolerance (n, %)	6 (85.7%)	1 (14.3%)	-

C-section (n, %)	6 (54.5%)	5 (45.5%)	-
Positive Group B streptococcus (n, %)*	5 (50.0%)	5 (50.0%)	-
Positive bacterial vaginosis (n, %)*	8 (66.7%)	4 (33.3%)	-
Gestational hypertension (n, %)	4 (50.0%)	4 (50.0%)	-
Preterm birth (n, %)	7 (77.8%)	2 (22.2%)	-

†Median (interquartile range) for non-normally distributed variables.
*For those tested.
** One outlier was removed (HbA1c = 7.6%) from the serum [25-OHD] < 50 nmol/L group. If outlier was not removed, mean HbA1c is 6.0 ± 0.6 and 5.6 ± 0.4% in the < 50 and ≥ 50 nmol/L groups, respectively (P = 0.039).

Table 5.7 Relationships of glycemia indices and variables of interest in bivariate analyses

Variable	n	Correlation coefficient*	P
2-hr 75-g OGTT PG			
Maternal age (years)†	35	0.263	0.277
Weight (kg)	35	0.429	0.067
BMI (kg/m^2)	35	0.284	0.239
HbA1c			
Maternal age (years)†	35	0.088	0.625
Weight (kg)	**35**	**0.430**	**0.012**
BMI (kg/m^2)	**35**	**0.521**	**0.002**

Pearson's correlation coefficient except where indicated by †.
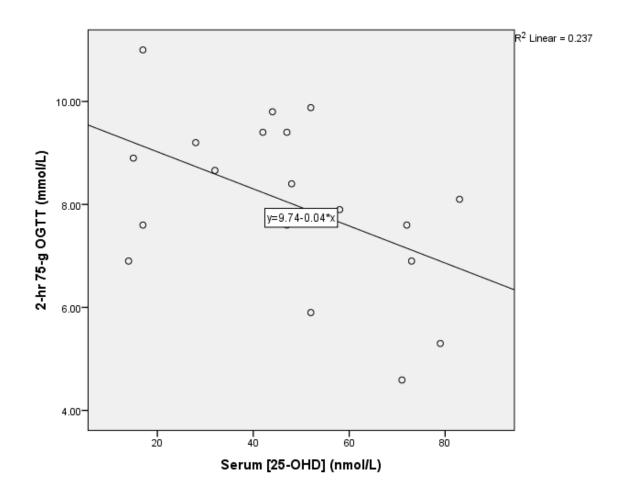*†Spearman's correlation for non-normally distributed variables.*

Figure 5.1 Scatterplot of serum 25-hydroxyvitamin D concentrations [25-OHD] and 2-hour plasma glucose after oral glucose tolerance testing (2-hr 75-g OGTT PG) from 19 women with gestational diabetes.

5.5. Discussion

5.5.1. Overview

During pregnancy, the fetus is dependent on the mother for vitamin D.[23] Vitamin D deficient mothers are unable to pass adequate serum [25-OHD] to their fetuses, therefore increasing the risk of poor bone density and childhood rickets[3] and they are at higher risk for pregnancy complications.[7] Over half of the women (51.4%) with GDM in our study were deficient in serum [25-OHD], thus supporting vitamin D deficiency as public health issue.

High rates of vitamin D deficiency and insufficiency existed despite the use of prenatal multivitamins containing approximately 400 IU cholecalciferol. These results parallel other studies that find a high prevalence of vitamin D deficiency and insufficiency among pregnant and lactating women in Canada.[24-28]

5.5.2. Glycemia indices

We report an inverse relationship between serum [25-OHD] and 2-hr PG on the 75-g OGTT in women with GDM. Women who were vitamin D deficient were more likely to have higher 2-hr PG on the 75-g glucose tolerance test, suggesting a worsened insulin secretion deficiency. To our knowledge, this is the first Canadian study to report this association. Vitamin D deficient women had a trend for higher glycated A1c levels than women who were insufficient or sufficient. These observations support the results of other studies regarding the role of vitamin D in glucose metabolism in women with GDM.

In a study involving 147 Australian women diagnosed with GDM, 47% of women had serum [25-OHD] $\leq$ 50 nmol/L, and serum [25-OHD] concentrations were inversely

associated with fasting glucose, 2-hr glucose levels on the 75-g OGTT ($P = 0.05$ for both) and log[HbA1c] ($P < 0.001$).[29]

In a study of 266 pregnant Spanish women, 59% of women had serum [25-OHD] < 50 nmol/L, and serum [25-OHD] concentrations were inversely correlated with HbA1c, homeostasis model assessment of insulin resistance (HOMA-IR), serum insulin, and fasting and 1-hr glucose levels on the 100-g OGTT ($P < 0.001$).[30]

One double-blind randomized controlled trial supplemented 27 women with GDM with 50,000 IU cholecalciferol twice during a 6 week period. Women who were supplemented had a significant decrease in concentrations of fasting plasma glucose ($P < 0.001$) and serum insulin levels ($P = 0.01$) and HOMA-IR ($P < 0.001$) and a significant increase in the Quantitative Insulin Sensitivity Check Index ($P = 0.003$) compared with placebo (n = 27).[31]

In a subsequent randomized controlled trial by Asemi and colleagues (2014), 28 women with GDM were randomized to receive 1,000 mg calcium daily along with 50,000 IU cholecalciferol twice during a 6 week period. Women who were supplemented had a significant decrease in concentrations of fasting plasma glucose ($P < 0.001$) and serum insulin levels ($P = 0.02$) and HOMA-IR ($P = 0.001$) and a significant increase in the Quantitative Insulin Sensitivity Check Index ($P = 0.003$) compared with placebo.[32]

The upcoming DALI trial intends to address the possibility that vitamin D supplementation (1,600 IU/day) may reduce the risk of GDM in overweight and obese European women.[33]

In our study, both weight and BMI significantly affected [25-OHD] concentrations as well as HbA1c, suggesting that body weight is a likely confounder

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given that obesity is a risk factor for GDM. However, age, weight, and BMI showed no significant relationship with 2-hr 75-g plasma glucose. While weight and BMI can influence longer-term glucose control, vitamin D may augment the demand for higher insulin requirements during pregnancy.

5.5.3. Risk factors for vitamin D deficiency

Manitoba is located on a latitude between 49-60°N, where supplement and dietary sources of vitamin D are relied on for much of the year. Poor vitamin D status during pregnancy is multifactorial, however it can be due to the latitude, limited sun and skin exposure, and dark skin pigmentation of many women.[34] In our study, prenatal multivitamins were important for preventing vitamin D deficiency, however, the amount of cholecalciferol in prenatal multivitamins is inadequate to meet serum [25-OHD] concentrations ≥ 75 nmol/L. Women who cannot tolerate or afford prenatal vitamins are at high risk for vitamin D deficiency.

Limited consumption or avoidance of vitamin D fortified products (including lactose intolerance, milk allergy, or veganism) can also increase risk for deficiency.[35] In our study, women with lactose intolerance had mean serum [25-OHD] concentrations just above the cut-off point for severe deficiency. Almost 2 out of 3 women had very poor estimated vitamin D intakes (< 100 IU/day), subsequently these women had lower serum [25-OHD] concentrations.

Because vitamin D is lipid soluble, heavier individuals tend to sequester vitamin D in fat tissues and have lower vitamin D status.[36,37] Women with obese BMI values had 39% lower serum [25-OHD] concentrations than women with a normal or overweight

BMI values. An inverse correlation was also seen for serum [25-OHD] and weight, which supports the impact that weight has on vitamin D status.

Recently, age has been cited as risk factor for vitamin D deficiency in pregnancy.[38,39] Older pregnant women might have better dietary habits and are more likely to take prenatal vitamins. They might also spend more time outdoors, hence have more exposure to sunshine. Hence, younger women may benefit from prenatal nutrition counselling. Strategies for improving vitamin D status among pregnant women include increased education and vitamin D supplementation.[40]

5.5.4. Screening for vitamin D deficiency and supplementation

Screening is recommended for women who are at high-risk for deficiency.[41-43] Given that over half (51.4%) of women in this study were vitamin D deficient, women living at northern latitudes should be considered for routine screening for vitamin D deficiency. Perhaps screening may take place upon initial presentation of pregnancy or at the time of OGTT.

The recommended dosage of vitamin D during pregnancy varies depending on guidelines.[23,34,35,43] According the Endocrine Society (2011), at least 1,500 to 2,000 IU/day may be needed to maintain serum [25-OHD] above 75 nmol/L in pregnant and lactating women.[23] Doses of 4,000 IU/day have been shown to safely achieve [25-OHD] above 75 nmol/L.[44,45] In addition, a dose of 10,000 IU/day for five months in pregnancy did not elevate levels into toxic range (> 225 nmol/L).[46] Based on the evidence, a daily dose of 2,000 to 4,000 IU/day of cholecalciferol may be used to safely achieve sufficient serum [25-OHD].

5.5.5. Incidence of GDM in Canada

GDM is one of the most common complications of pregnancy, affecting 3.7% in the non-Aboriginal (multi-ethnic) population and 8 to 18% in the Aboriginal population in Canada,[47] and it carries long-term risks of obesity and T2DM for children born to mothers with GDM.[48] The impairment of insulin secretion and action during GDM persists postpartum and increase the risk of T2DM later in life, with the highest risk seen during the first 5 years postpartum. It is estimated that 35 to 60% of women with GDM will develop T2DM within 10 years.[49,50] In our study, almost one in three women (22.9%) were diagnosed with T2DM at a median of 18 weeks postpartum.

Hence, if sufficient serum [25-OHD] concentrations reduce the incidence or severity of GDM, this could have considerable significance to public health.

5.6. Study limitations

Since this was a chart review, there are some limitations to be considered. Data from the chart may have been incomplete. The study was limited by the sample size, which did not allow for statistical comparisons of serum [25-OHD] among the three categories of vitamin D status. In addition, education, ethnicity, and indices of insulin sensitivity were not collected, and may be potential confounding factors. Because this is a retrospective study, we cannot assume causation.

5.7. Conclusion

Screening for vitamin D deficiency should be considered during routine blood work or at the time of OGTT, with subsequent treatment for women found to be

deficient. Vitamin D supplements are relatively inexpensive and easily tolerated. In addition to a prenatal multivitamin, daily vitamin D supplementation should be encouraged to prevent vitamin D deficiency. Alternatively, the amount of cholecalciferol in prenatal supplements may be increased.

5.8. Future studies

Randomized controlled trials are needed to test whether vitamin D supplementation during pregnancy affects the risk for developing GDM and thereby leads to improved maternal and neonatal outcomes.

5.9. Acknowledgements

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Chapter 6: Additional Findings from the Retrospective Chart Review

6.1. Relationships of [25-OHD] with other variables of interest

6.1.1. Induction of labour and serum [25-OHD]

There was no significant difference in the mean serum [25-OHD] for women who were induced (51.7 nmol/L, SD = 22.9) when compared with women who were not induced (50.8 nmol/L, SD = 25.8); t(32) = 0.099, $P = 0.922$.

6.1.2. C-section incidence and serum [25-OHD]

There was no significant difference in the mean serum [25-OHD] for women who delivered via C-section (45.5 nmol/L, SD = 22.5) when compared with women who delivered vaginally (54.3 nmol/L, SD = 24.6); t(31) = -1.002, $P = 0.324$.

6.1.3. Gestational HTN incidence and serum [25-OHD]

There was no significant difference in the mean serum [25-OHD] for women who developed gestational HTN (48.3 nmol/L, SD = 27.4) when compared with women who did not develop gestational HTN (52.7 nmol/L, SD = 23.3); t(32) = 0.456, $P = 0.651$.

6.2. Blood pressure and serum [25-OHD]

6.2.1. Systolic blood pressure

There was no significant correlation between systolic blood pressure and serum [25-OHD] (r_s = -0.172, n = 31, $P = 0.354$).

6.2.2. Diastolic blood pressure

There was a no significant correlation between diastolic blood pressure and serum [25-OHD] (r_s = -0.186, n = 31, $P = 0.317$).

6.3. Bacterial infections and serum [25-OHD]

6.3.1. Group B streptococcus

There was no significant difference in the mean serum [25-OHD] for women who tested positive for group B streptococcus (50.9 nmol/L, SD = 31.8) when compared with women who did not develop group B streptococcus (56.4 nmol/L, SD = 21.2); t(25) = -0.536, $P = 0.597$.

6.3.2. Bacterial vaginosis

There was no significant difference in the mean serum [25-OHD] for women who tested positive for bacterial vaginosis (43.8 nmol/L, SD = 20.2) when compared with women who did not develop bacterial vaginosis (53.3 nmol/L, SD = 24.8); t(20) = -0.997, $P = 0.331$.

6.3.3. Chlamydial, gonorrheal, and trichomoniasis infections

One woman with [25-OHD] < 50 nmol/L tested positive for chlamydia. There were no cases of gonorrheal infections. Three women (13.0%) tested positive for trichomonas, all of which had serum [25-OHD] < 50 nmol/L. These small sample sizes limit the use of statistical tests.

6.4. Postpartum T2DM and serum [25-OHD]

There was no significant difference in the mean serum [25-OHD] for women who tested positive for T2DM postpartum (50.3 nmol/L, SD = 25.7) when compared with women who did not develop T2DM postpartum (53.1 nmol/L, SD = 24.1); t(33) = 0.291, $P = 0.773$.

6.5. Birth outcomes

6.5.1. Infant birth weight

After controlling for anemia, nicotine use, and BMI, infant birth weight was inversely associated with gestational HTN but not with serum [25-OHD] (Table 6.1).

6.5.2. Preterm birth

There was a significant difference in the mean serum [25-OHD] for women who delivered before 37 weeks (37.9 nmol/L, SD = 19.6) when compared with women who delivered at normal gestational age (57.50 nmol/L, SD = 23.7) conditions; $t(33) = 2.224$, $P = 0.033$. However, after controlling for anemia, nicotine use, and gestational HTN, preterm delivery was not significantly associated with serum [25-OHD] (Table 6.2).

Women who had a very high BMI were more likely to deliver early. There was a significant difference in the mean BMI for women who delivered preterm (40.6 kg/m^2, SD = 4.1) when compared with women who delivered at term (33.3 kg/m^2, SD = 6.0); $t(33) = -3.386$, $P = 0.002$.

6.5.3. Apgar scores

As mentioned previously, at the 1-minute Apgar test, scores of 4-6 indicate that some assistance for breathing might be required. At the 5-minute Apgar test, if the score is under 7, the baby will continue to be monitored and retested every 5 minutes for up to 20 minutes.

Seven infants (21.2%) scored less than 7 on the 1-minute Apgar test. Three of these infants were delivered by mothers who had serum [25-OHD] < 50 nmol/L. None of the infants scored less than 7 at the 5-minute Apgar test.

6.6. Early-onset GDM

Based on the available results for the 50-g and/or 75-g OGTT, 22 women (62.9%) were diagnosed with GDM before 24 weeks gestation. Six women (17.1%) were diagnosed after 24 weeks gestation. The remaining seven women (20%) did not have OGTT information available or could have had a history of GDM and were referred to the clinic without formal testing for GDM. Compared to women diagnosed later in their pregnancy, GDM prior to 24 weeks was not associated with a greater BMI (34.2 kg/m^2, SD = 6.8 vs 35.0 kg/m^2, SD = 5.7); (t)29 = 0.107, P = 0.916 or birth weight (3373.1 g, SD = 610.1 vs 3562.8 g, SD = 764.5); t(27) = 0.645, P = 0.524 (Table 6.3).

Preterm delivery was more common in women with early-onset GDM. Six out of seven (85.7%) preterm births were delivered by women with early-onset GDM (< 24 weeks gestation). Induction of labour was more common in this group, which may partially explain the higher incidence of preterm delivery.

Of the eight women who developed gestational HTN, five women (62.5%) were diagnosed early with GDM. One woman had pre-existing HTN and was found to test positive for GDM early as well.

A total of 10 newborns were admitted to the neonatal intensive care unit (NICU). Most of these infants (90.0%) were delivered by women with early-onset GDM. Reasons for admission in the early-onset GDM group include neonatal hypoglycemia (2 cases), large for gestational age (1 case), respiratory distress syndrome (1 case), and jaundice (1 case). One infant born to a woman with early-onset GDM suffered from shoulder dystocia. Five infants (29.4%) delivered by women with early-onset GDM scored less than 7 on the 1-minute Apgar test.

In this study, women with early-onset GDM were more likely to: develop gestational HTN, require insulin therapy, have induction of labour, deliver early (< 37 weeks), deliver by C-section, and develop T2DM postpartum. Also, most cases of NICU admission were from this group. Women with early-onset GDM were more likely to test positive for group B streptococcus and bacterial vaginosis. (Table 6.3). Based on these findings, women with early-onset GDM are a high-risk subgroup of pregnant women. It may be plausible that these women have undiagnosed pregestational T2DM, especially if tested positive for GDM in the first trimester, yet there is a lack of consensus with regards to T2DM diagnosis in pregnancy. However, "overt diabetes" can be diagnosed in the first trimester according to the International Association of Diabetes and Pregnancy Study Groups (2010) if fasting plasma glucose is ≥ 7.0 mmol/L, 75-g OGTT 2-hr plasma glucose is ≥ 11.1 mmol/L, or HbA1c is ≥ 6.5%.[1] Given the higher rate of pregnancy complications, women with early-onset GDM should be considered and managed as having pregestational T2DM. Early screening in women at high risk for T2DM would allow for prompt intervention and earlier metabolic control, benefitting both mother and child.

In a 2000 study, women with GDM diagnosed before 24 weeks (n = 65) were likely to be hypertensive (18.5% vs 5.9%; $P = 0.006$) and had higher glycemic values and need for insulin therapy (33.9% vs 7.1%, $P = 0.0001$) than those in whom diabetes developed later (n = 170).[2] All the cases of neonatal hypoglycemia (n = 4) and all perinatal deaths (n = 3) were within this group ($P = 0.005$ and $P = 0.01$), respectively. A recent poster found that women with early diagnosis of GDM (< 24 weeks gestation)

were more likely to deliver prior to 37 weeks ($P < 0.001$), have a greater BMI ($P < 0.01$), and have smaller birth weight infants ($P < 0.01$).[3]

Individuals with diabetes have a higher risk of infections, which may explain why women with early onset-GDM had a higher incidence of group B streptococcus and bacterial vaginosis infections.[4]

6.7. Relationships of calcium with other variables of interest

Calcium intakes were estimated using common food sources (e.g. dairy) and are reported from food only.

Women who consumed less daily calcium delivered their infant slightly earlier. There was no statistically significant difference in the mean gestational age at delivery for women who consumed < 300 mg/day (37.3 weeks, SD = 1.6) when compared with women who consumed > 300 mg/day (38.2 weeks, SD = 1.9); t(30) = -1.436, $P = 0.161$.

Women who consumed less daily calcium delivered infants who weighed slightly less. The mean infant birth weight for women who consumed < 300 mg/day (3416 g, SD = 758) when compared with women who consumed > 300 mg/day (3657 g, SD = 369); t(28) = -0.901, $P = 0.375$.

There was no statistically significant difference in systolic blood pressure of women who consumed < 300 mg/day (117 mmHg, SD = 12.2) when compared with women who consumed > 300 mg/day (110 mmHg, SD = 8.1); t(26) = 1.528, $P = 0.139$.

Although our results are not statistically significant (likely due to a low sample size), future studies need to address whether women who consume very low amounts of

calcium (< 300 mg/day) tend to deliver earlier, have lower birth weight infants, and have higher systolic blood pressure.

All women (n = 7) who reported lactose intolerance consumed an estimated < 300 mg/day. Three out of five women (60%) who report tolerating lactose consumed more estimated calcium (> 300 mg/day). Because calcium is found in many food sources containing lactose, it is of no surprise that women who report lactose intolerance consume less dietary calcium.

Table 6.1 Multiple linear regression for potential explanatory variables of infant birth weight

Variable	Coefficient	95% confidence interval	*P*
Nicotine use	177.286	-335.497 to 690.069	0.484
Anemia	-314.653	-1104.225 to 474.919	0.420
BMI	25.317	-12.331 to 62.965	0.179
HTN	**578.335**	**73.509 to 1083.160**	**0.026**
[25-OHD]	3.538	-7.850 to 14.925	0.529

Table 6.2 Multiple linear regression for potential explanatory variables of preterm birth

Variable	Coefficient	95% confidence interval	*P*
Nicotine use	-0.079	-0.410 to 0.253	0.632
Anemia	-0.358	-0.876 to 0.160	0.420
HTN	-0.124	-0.451 to 0.203	0.444
[25-OHD]	-0.005	-0.011 to 0.002	0.170

Table 6.3 Maternal and clinical characteristics of participants by diagnosis of GDM

Variable*	GDM < 24 weeks (mean ± SD)	GDM ≥ 24 weeks (mean ± SD)	P
Number (n, %)	22 (78.6%)	6 (21.4%)	-
Maternal age (median (IQR), years)†	26.5 (11)	33.5 (9)	0.097
Latitude (median (IQR), degrees)†	53 (0)	49 (4)	0.026
Weight (kg)	88.5 ± 18.3	101.4 ± 15.3	0.129
Height (cm)	161.1 ± 5.9	168.6 ± 8.6	0.019
BMI (kg/m^2)	34.2 ± 7.2	35.8 ± 5.5	0.628
Serum [25-OHD] (nmol/L)	55.4 ± 23.9	46.8 ± 19.3	0.429
Gestational age at delivery (weeks)†	38.5 (4.0)	37.5 (2.0)1	0.090
Infant birth weight (g)	3411 ± 619	3549 ± 854	0.676
Macrosomia (n, %)	2 (50.0%)	2 (50.0%)	-
Required insulin (n, %)	17 (77.3%)	5 (22.7%)	-
T2DM diagnosis postpartum (n, %)*	5 (100%)	0 (0%)	-
Reports prenatal multivitamin (n, %)	16 (76.2%)	5 (23.8%)	-
Reports lactose intolerance (n, %)	4 (66.7%)	2 (33.3%)	-
Cesarean section (n, %)	8 (80.0%)	2 (20.0%)	-
Positive Group B streptococcus (n, %)*	7 (77.8%)	2 (22.2%)	-
Positive bacterial vaginosis (n, %)*	9 (90.0%)	1 (10.0%)	-
Gestational hypertension (n, %)	5 (83.3%)	1 (16.7%)	-
Induction of labour (n, %)	13 (76.5%	4 (23.5%)	-

Preterm birth (n, %)	6 (85.7%)	1 (14.3%)	-
NICU admission (n, %)	9 (90.0%)	1 (10.0%)	-

†Median (interquartile range) for non-normally distributed variables.
*For those tested.

6.8. References

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Chapter 7: General Discussion

7.1. Summary

The purpose of this study was to examine calcium and vitamin D nutrition from a clinician perspective of care (Part 1) and from a patient standpoint of health (i.e. nutritional status) (Part 2).

The objectives of this two-part study were to:

1) Investigate the nutrition-related knowledge, opinions, and clinical practices of FPs towards prenatal calcium and vitamin D.

2) Determine what barriers exist in providing calcium and vitamin D nutrition advice to prenatal patients.

3) Determine the prevalence of meeting a predefined cut-off serum [25-OHD] for vitamin D sufficiency ($\geq$ 75 nmol/L) in a cohort of pregnant women with GDM.

4) Assess serum [25-OHD] and its associations with serum [25-OHD], glycemic indices, and birth outcomes.

5) Determine the impact of maternal factors on serum [25-OHD].

In Part 1, most physicians had good knowledge regarding calcium dosage, calcium and vitamin D contents in one cup (250 ml) of cow's milk, and were aware of the poor intakes among Canadian women. Interestingly, more female physicians scored incorrectly on the content of calcium and vitamin D in one cup (250 ml) of cow's milk. Because women are at a higher risk for osteoporosis, it is thought that women might have a better nutrition knowledge. The results from this study showed that this stereotype is

not true. Less than two out of three physicians scored correctly on the major risk factors for vitamin D deficiency. Only 8.1% of family physicians agreed with the Institute of Medicine (2010)[1] and Health Canada (2011)[2] recommendation of 600 IU vitamin D/day. The majority, (55.5%) thought that 800-1,000 IU/day is adequate according to Osteoporosis Canada (2010)[3]. Although the respondents agreed with a higher daily dose, the majority are not actually recommending vitamin D supplements. Hence, a knowledge translation discrepancy exists. Perhaps this can be due to a lack of consensus on "optimal" vitamin D status and multiple dietary recommendations for vitamin D, which is further compounded by an overall discouragement of routine screening for vitamin D deficiency.

Over half of respondents perceived receiving nutrition education as part of continuing medical education as very important or important. "More urgent issues", "lack of time", and "forgetting to do so" were cited as the top three perceived barriers to delivery of calcium and vitamin D advice. Nutrition education of younger physicians (those practicing for 20 years or less) is particularly concerning given that they were more likely to cite "unsure of what to recommend". This indicates that there is a gap in nutrition education for clinicians. FPs would benefit from current practice-based nutrition education on key nutrients during pregnancy. Delivery of nutrition care (i.e. nutrition counselling) should be simple and easy for clinicians. If FPs are unable to deliver proper nutrition care, due to other issues such as time constraints, a partnership with nearby RDs should be made easily accessible. Information packages on key nutrients during pregnancy could be provided at the appointment when patients initially present with pregnancy prior to referral to an obstetrician or midwife for medical care.

In Part 2, vitamin D deficiency was apparent in our cohort of women with GDM, with the mean serum [25-OHD] at 52.5 nmol/L. Over half of women (51.4%) were vitamin D deficient (defined as [25-OHD] < 50 nmol/L), and 28.6% of women were insufficient (defined as [25-OHD] 50-74 nmol/L). Only two out of 10 women had vitamin D concentrations that were considered sufficient (defined as [25-OHD] ≥ 75 nmol/L). This is worrisome because vitamin D is required for normal fetal skeletal growth during pregnancy.[1] In addition, vitamin D deficiency is associated with important pregnancy outcomes including the development of GDM and preeclampsia, as well as bacterial vaginosis, and may impact birth weight and delivery by C-section.[4] Vitamin D has the potential to modify glucose metabolism by improving insulin sensitivity and output,[5-7] which has important implications in the setting of GDM and risk of T2DM postpartum. Women with GDM were chosen as our cohort because many studies have shown a strong and consistent association between low serum [25-OHD] and GDM.[4] However, only a handful of studies have looked at glycemic control exclusively in women the GDM.[8-11]

In the present study, 2-hr 75-g plasma glucose was inversely correlated with [25-OHD] ($P < 0.05$). A statistically significant association was found between [25-OHD] and 2-hr glucose from the 75-g OGTT (r = -0.487, $P = 0.035$), but not with the fasting blood glucose or 1-hr glucose or glycated hemoglobin. Women with [25-OHD] < 50 nmol/L had higher 2-hr 75-g plasma glucose levels than women with [25-OHD] > 50 nmol/L (8.8 ± 1.2 mmol/L vs 7.0 ± 1.7 mmol/L, $P = 0.015$). Furthermore, women who delivered before 37 weeks had significantly lower mean serum [25-OHD] (37.9 ± 19.6 nmol/L) when compared with women who delivered at normal gestational

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age (57.5 ± 23.7 nmol/L, $P = 0.033$). Hence, if sufficient serum [25-OHD] concentrations reduce the incidence or severity of GDM, this could have considerable implications for the children born to mothers with GDM and long-term risk of T2DM in the mother. In addition, women who were diagnosed early with GDM had more pregnancy complications than women who were diagnosed later in their pregnancy. Women who are at a high risk for GDM should be considered for early GDM screening and managed as having pregestational T2DM. Early screening in women at high risk for T2DM would allow for prompt intervention and earlier metabolic control, benefitting both mother and child. Adequate vitamin D has the potential to mitigate some of the pregnancy complications in women with early-onset GDM. Further studies are required to investigate if vitamin D can reduce the incidence or severity of pregnancy complications in women with early-onset GDM.

Poor vitamin D status during pregnancy is multifactorial, however it can be due primarily to latitude, limited sun and skin exposure, and dark skin pigmentation.[1,12] In Canada, especially in Northern Canada, vitamin D in the form of food and supplements are relied on for most of the year due to inadequate UVB radiation as well as cold temperatures necessitating warm clothing and therefore limiting skin exposure to the sun. Age[13,14] and body weight[15,16] have been implicated as factors affecting serum [25-OHD] concentrations. Older individuals may be more likely to follow nutrition recommendations and take supplements and hence, have better vitamin D concentrations.[13,14] Fat cells sequester the fat soluble vitamin D, resulting in lower serum vitamin D concentration.[15,16] Our results support these findings. Age was correlated positively with serum [25-OHD] ($P < 0.05$), however maternal weight, and body mass

index (BMI) were inversely correlated with [25-OHD] ($P < 0.05$). Latitude was not significantly correlated with serum [25-OHD] in our sample, which indicates that all women in Manitoba are at considerable risk for vitamin D deficiency.

Women who were not taking prenatal vitamins or were lactose intolerant had significantly lower vitamin D concentrations, demonstrating the influence of dietary and supplemental vitamin D intakes.[1] Our findings indicate that certain maternal factors may predispose pregnant women to vitamin D deficiency, which in turn suggests that vitamin D may influence glucose metabolism. Prenatal vitamins containing vitamin D improved serum [25-OHD] concentrations, but higher doses may be required to achieve sufficient vitamin D levels.

Pregnant women are seen by their FP (or nurse practitioner) prior to being sent to an obstetrician or midwife for prenatal care. If GDM is diagnosed, pregnant women are referred to an endocrinologist for diabetes care. Since FPs provide initial prenatal care, it seems most appropriate for them to discuss basic nutrition (like calcium and vitamin D) prior to being referred to an obstetrician or midwife. There is an opportunity for FPs to screen and treat for vitamin D deficiency at the beginning of pregnancy where the benefits of adequate vitamin D can start sooner. Perhaps this may lead to an overall reduced risk of developing GDM.

7.2. Limitations

Part 1: Since this was a self-administered survey, our results were subject to a volunteer bias, which could be the reason for the low response rate. Physicians with an interest in nutrition were, perhaps, more likely to respond to the survey. Another potential

limitation to consider is social desirability response bias, whereby respondents give socially acceptable responses rather than reporting their actual opinions or practices. It is a known challenge to survey physicians due to their busy work schedules. An electronic survey may have improved response rate, however, email information was not available. Further studies using a qualitative approach (such as focus groups) may help to further understand the clinician point of view.

Part 2: Given that this was a chart review, data from the chart may have been incomplete or missing. This study was limited by the sample size, which did not allow for statistical comparisons of serum [25-OHD] among the three categories of vitamin D status. In addition, education, ethnicity, and indices of insulin sensitivity were not collected, and may be potential confounding factors. Because this is a retrospective study, we cannot assume causation. Despite the low sample size, we found outcomes that parallel previous studies which further support that vitamin D indeed influences glucose metabolism. A larger sample size would permit for further statistical analyses and increase the strength of statistical tests.

7.3. Implications of findings

The results from this study have several important implications. Nutrition is an evolving field that requires continuous updating. Recommendations and guidelines are constantly changing. Consequently, it may be confusing and overwhelming for busy health professionals. Delivery of nutrition care should be simple. Nutrition education should be part of continuing education on an annual basis. Webinars, online and paper resources may also be avenues to provide current, evidence-based nutrition

recommendations. Nutrition should be given importance during medical training.

Partnership with local RDs can enhance delivery of nutrition care. For example, dietitians

may be employed at clinics. Given the importance of adequate calcium and vitamin D

during pregnancy, perhaps a standardized handout can be easily made available to

clinicians. For vitamin D, evidence is accruing for its role in maintaining glucose

homeostasis. GDM is a growing problem in Canada.[17] Therefore, consideration should be

given to testing serum [25-OHD] at time of the OGTT or earlier. Vitamin D may

augment the demand for higher insulin requirements during pregnancy and perhaps

reduce the risk for GDM. Randomized controlled trials are needed to test whether vitamin

D supplementation during pregnancy affects the risk for developing GDM and thereby

leads to improved maternal and neonatal outcomes. The DALI trial will bring

clarification to this question.[18]

Although routine screening is not currently recommended in Manitoba[19], based on

our results, screening for vitamin D deficiency should be considered during routine blood

work or at time of OGTT, with subsequent treatment for women found to be deficient. As

mentioned previously, there are few foods that provide adequate vitamin D and many

women have dietary restrictions (such as lactose intolerance) that prohibits dairy intake.

Therefore, vitamin D supplements are very important for achieving adequate serum [25-

OHD]. Vitamin D supplements are relatively inexpensive and easily tolerated. In addition

to a prenatal vitamin, daily vitamin D supplementation should be encouraged to prevent

vitamin D deficiency. Clinicians should be encouraged to follow the Winnipeg Regional

Health Authority (2012) recommendation of 2,400 IU/day for pregnant and lactating

women.[20] This amount would come from vitamin D supplementation (2,000 IU) and the

remaining from a prenatal multivitamin (400 IU). This is a very safe and reasonable recommendation. If this daily dose was followed, it's likely that the level of vitamin D deficiency would not be as severe in our cohort of women with GDM. Alternatively, the amount of cholecalciferol in prenatal supplements may be increased.

Efforts made to increase awareness of vitamin D will help to bring attention to vitamin D. For example, public awareness through the media can improve the knowledge of the importance of vitamin D. Throughout the years, folic acid has been promoted as a key vitamin during pregnancy. Almost all (92.7%) physicians indicated that they "always" recommend a folic acid containing prenatal vitamin. Given the impact that vitamin D has on human health, vitamin D should be given the same value as folic acid during pregnancy.

Vitamin D deficiency in pregnancy is common in many industrialized countries despite vitamin D fortification of some foods and national dietary intake recommendations for deficiency prevention.[21] Although vitamin D fortification is mandatory for some foods in Canada,[22] including milk and margarine, perhaps a higher amount of vitamin D should be added, especially if the target serum [25-OHD] is 75 nmol/L.[23] Given that Health Canada (2011)[2] follows the Institute of Medicine's 2010 recommendation of 600 IU/day[1], it is likely impossible to achieve 75 nmol/L, since the Institute of Medicine's recommended cut off of adequacy for serum [25-OHD] is 50 nmol/L.[1] Therefore, consideration should be made to increasing vitamin D intakes through vitamin D supplements. This is especially important for women who are lactose intolerant and cannot tolerate dairy products.

7.4. Conclusion

FPs are the backbone of the community health care system, and it is essential to study their knowledge and opinions, behaviours, and concerns. Part of medical care during pregnancy includes basic dietary advice and treatment of nutritional deficiencies. This is the first Canadian study to examine the knowledge, opinions, and clinical practices as well as identify what barriers exist for FPs in providing calcium and vitamin D advice during pregnancy. Opportunities to improve knowledge of calcium and vitamin D nutrition should be available through continuing medical education. Furthermore, access to calcium and vitamin D information should be made easily accessible to clinicians and should be discussed at time of initial presentation of pregnancy. Given the high rate of vitamin D deficiency in our cohort of pregnant women with GDM, screening for vitamin D deficiency would be beneficial during routine blood work or at time of OGTT, with subsequent treatment for women found to be deficient. Vitamin D deficiency is a relatively inexpensive and easily curable health problem. In addition to a prenatal vitamin, daily vitamin D supplementation should be encouraged to prevent vitamin D deficiency. Alternatively, the amount of cholecalciferol in the food supply or prenatal supplements may be increased.

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Appendices

Appendix A: Letter of Consent

Faculty of Human Ecology

Human Nutritional
Sciences

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UNIVERSITY
OF MANITOBA

Title of Study: "Knowledge, Attitudes, and Clinical Practices Regarding Prenatal Calcium and Vitamin D Nutrition among Family Physicians in Manitoba"

Letter of Consent

Hello,

My name is Colleen Rogers. I am a Dietitian and graduate student being supervised by Dr. Carla Taylor with the University of Manitoba in the Department of Human Nutritional Sciences.

Background: Family Physicians are trained to provide prenatal medical care, including basic dietary education. However, the knowledge, attitudes, and clinical practices regarding prenatal nutrition in this group remain to be studied. Our decision to target calcium and vitamin D during pregnancy will provide further clarity to this area. This survey is part of a mixed-methods study investigating calcium and vitamin D nutrition during pregnancy in Manitoban women.

Purpose: The purpose is to survey practicing Family Physicians in Manitoba with respect to their knowledge, attitudes, and clinical practices regarding prenatal calcium and vitamin D nutrition.

Study Procedures: To participate, you are being asked to answer the attached short questionnaire that will take about **5-10 minutes to complete**. This questionnaire will determine your current nutrition knowledge, attitudes, and clinical practices about calcium and vitamin D nutrition during pregnancy. Once you have completed the questionnaire, you will return it to the Principal investigator using the pre-paid return envelope. ***Please return the completed questionnaire by the end of March 2014.***

Study Risks & Benefits: There are no risks associated with answering these questions. There may or may not be direct benefit to you from participating in this study. You, your patients, or colleagues may benefit from the outcomes of this research. Benefits include identifying knowledge gaps in the nutrition knowledge of Family Physicians. These findings may be used to enhance the education regarding prenatal nutrition among Family Physicians, with the goal to improve the health of mothers and their offspring living in Manitoba. ***Complete the survey and enter to win an iPad!***

Feedback to Participants: If desired, you may obtain the answers to the knowledge-based questions. To do so, please visit Dr. Taylor's website (http://umanitoba.ca/faculties/human_ecology/staff/hn_sciences/160.html) after May 1, 2014.   A total of 500 Family Physicians across Manitoba will be asked to complete this survey.

REMINDER: Participation in this study is voluntary; questionnaires will remain anonymous, and cannot be tracked back to the respondent. Completing the questionnaire implies consent to participating in the study. Please remember that any data pertaining to you, as an individual participant, will be kept confidential. Once all of the data are collected and analyzed, it will be part of my MSc Thesis. We plan to share this information through research documents,

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conferences, presentations, and articles.

This research has been approved by the Joint-Faculty Research Board of Ethical Review at the University of Manitoba. For questions about your rights as a research participant, you may contact the Human Ethics Coordinator at (204) 474-7122 or e-mail Margaret.bowman@umanitoba.ca. If you have any further questions, please contact the Principal Investigator at:

Colleen Rogers, RD, CDE, MSc Student
rogersc@cc.umanitoba.ca

Appendix B: Questionnaire

Knowledge, Attitudes, and Clinical Practices Regarding Prenatal Calcium and Vitamin D Nutrition among Family Physicians in Manitoba

Instructions: There are 32 questions. Please indicate your answer by putting a checkmark (√) in the box beside your response.

Abbreviations: mg = milligrams; IU = International Units; OTC = over the counter; RHA = Regional Health Authority

PART 1: CALCIUM

Q1. Approximately how many <u>prenatal patients</u> do you provide care for in a given month?
- ☐ 1-10
- ☐ 11-20
- ☐ 21 or more: Please indicate how many _____

Q2. Think about your <u>new</u> prenatal patients - do you <u>routinely</u> discuss calcium requirements with them?
- ☐ Yes
- ☐ No

Q3. <u>Within the last month,</u> have you suggested OTC <u>calcium supplements</u> to your prenatal patients?
- ☐ Yes
- ☐ No → (Skip to Q5)

Q4. (If Yes) What percentage of these patients did you suggest OTC calcium supplements to?
- ☐ <25%
- ☐ 25-75%
- ☐ >75%

Q5. Has the potential association between calcium supplements and cardiac events in postmenopausal women deterred you from suggesting calcium supplements to your prenatal patients?
- ☐ Yes
- ☐ Somewhat
- ☐ No

Q6. The recommended daily amount of calcium (from both food and dietary supplement intake) for pregnant women 19 to 50 years is:
- ☐ 500 mg
- ☐ 1000 mg
- ☐ 1500 mg
- ☐ Don't know

Q7. The amount of calcium and vitamin D in one cup (250 ml) of cow's milk is:
- ☐ 300 mg calcium, no vitamin D
- ☐ 300 mg calcium, 100 IU vitamin D
- ☐ 100 mg calcium, 300 IU vitamin D
- ☐ Don't know

Q8. The calcium dosage in popular OTC calcium supplements is:
- ☐ 200 mg
- ☐ 400 mg
- ☐ 500-600 mg
- ☐ 800-1200 mg
- ☐ Don't know

Q9. The majority of Canadian women 19 to 50 years are not meeting the current calcium requirement (from food and dietary supplement intake).
- ☐ True
- ☐ False
- ☐ Don't know

Q10. Low maternal dietary calcium intake (<600 mg/day) can increase the risk for preeclampsia, preterm delivery, or excessive maternal bone loss.
- ☐ True
- ☐ False
- ☐ Don't know

PART 2: VITAMIN D

Q11. Think about your <u>new</u> prenatal patients - do you <u>routinely</u> discuss vitamin D requirements with them?
- ☐ Yes
- ☐ No

Q12. <u>Within the last month,</u> have you suggested OTC <u>vitamin D supplements</u> to your prenatal patients?
- ☐ Yes
- ☐ No → (Skip to Q15)

Q13. (If Yes) What percentage of these patients did you suggest OTC vitamin D supplements to?
- ☐ <25%
- ☐ 25-75%
- ☐ >75%

Q14. (If Yes) How much daily OTC vitamin D supplement did you suggest?
- ☐ 400 IU
- ☐ 1,000 IU
- ☐ 2,000 IU
- ☐ 4,000 IU or more
- ☐ Other: Please indicate how much

  _____

Q15. Of the following vitamin D recommendations (from food and dietary supplement intake), what daily amount do you think is appropriate for your prenatal patients?
- ☐ 600 IU (Institute of Medicine, 2010 & Health Canada, 2011)
- ☐ 800-1,000 IU (Osteoporosis Canada, 2010)
- ☐ 1,500-2,000 IU (Endocrine Society, 2011)

Q16. Have you ordered a vitamin D test for your prenatal patients <u>within the last month</u>?
- ☐ Yes
- ☐ No → (Skip to Q18)

Q17. (If Yes) How many vitamin D tests have you ordered <u>within the last month</u>?
- ☐ 1-5 tests
- ☐ 6-10 tests
- ☐ 11 or more tests

Q18. How concerned are you about vitamin D deficiency during pregnancy?
- ☐ Not at all concerned
- ☐ A little concerned
- ☐ Somewhat concerned
- ☐ Quite concerned
- ☐ Extremely concerned

Q19. The Diagnostic Services of Manitoba (2012) guidelines for screening for vitamin D deficiency in Manitoba are appropriate.

☐ Definitely agree
☐ Probably agree
☐ Neither agree nor disagree
☐ Probably disagree
☐ Definitely disagree

Q20. Select the risk factor(s) that predispose pregnant women to vitamin D deficiency.

☐ Manitoba's latitude
☐ Limited sun exposure
☐ Dark skin pigmentation
☐ All of the above
☐ None of the above

Q21. Low maternal vitamin D status (<75 nmol/L) can increase the risk for gestational diabetes.

☐ True
☐ False
☐ Don't know

Q22. When providing prenatal care, which of the following barriers are relevant to giving (or not giving) calcium and/or vitamin D nutrition advice? Check all that apply.

☐ More urgent issues
☐ Lack of time
☐ Forget to do so
☐ Unsure of what to recommend
☐ I don't feel confident giving nutrition advice about calcium and vitamin D
☐ It's not part of my job
☐ Other:

_____

_

Q23. Have your prenatal patients reported any negative side effects from using calcium or vitamin D supplements?

☐ No
☐ Yes: Please describe

_____
_____

Q24. Please provide any additional comments that you may have regarding calcium and/or vitamin D during pregnancy.

_____

_____

_____

_____

_____

_____

PART 3: PRACTICE-BASED QUESTIONS

Q25. Do you recommend an OTC prenatal multivitamin supplement containing folic acid to your prenatal patients?
- ☐ Always
- ☐ Usually
- ☐ About half the time
- ☐ Seldom
- ☐ Never: Please explain why

_____

_____

_____

Q26. Do you refer pregnant patients to a Registered Dietitian for prenatal nutrition education?
- ☐ Yes
- ☐ No → (Skip to Q28)

Q27. (If Yes) How frequently have you referred your prenatal patients to a Registered Dietitian?
- ☐ Always
- ☐ Usually
- ☐ About half the time
- ☐ Seldom

Q28. How important is it to receive prenatal nutrition education as part of Continuing Professional Development for physicians?
- ☐ Very important
- ☐ Important
- ☐ Moderately important
- ☐ Of little importance
- ☐ Unimportant

Q29. Approximately how long have you been practicing Family Medicine?
- ☐ 1-5 years
- ☐ 6-10 years
- ☐ 11-15 years
- ☐ 16-20 years
- ☐ 21 years or more

Q30. In which (former) RHA district are you practicing?

Winnipeg RHA: ☐ Winnipeg ☐ Churchill

Northern RHA: ☐ Burntwood (e.g. Norway House, Cross Lake)

☐ NOR-MAN (e.g. Thompson, Flin Flon, The Pas)

Prairie Mountain Health: ☐ Brandon   ☐ Assiniboine (e.g. Neepawa, Killarney, Virden)   ☐ Parkland (e.g. Dauphin, Swan River, Grandview)

Interlake-Eastern RHA: ☐ Interlake (e.g. Selkirk, Gimli, Stonewall, Arborg)

☐ North Eastman (e.g. Beausejour, Pine Falls)

Southern Health-Santé Sud: ☐ Central (e.g. Portage La Prairie, Winkler, Morden)

☐ South Eastman (e.g. Steinbach, Ste. Anne)

Q31. The majority of your prenatal patients are from which (former) RHA district(s)? Check all that apply.

Winnipeg RHA: ☐ Winnipeg ☐ Churchill

Northern RHA: ☐ Burntwood (e.g. Norway House, Cross Lake)

☐ NOR-MAN (e.g. Thompson, Flin Flon, The Pas)

Prairie Mountain Health: ☐ Brandon

☐ Assiniboine (e.g. Neepawa, Killarney, Virden)

☐ Parkland (e.g. Dauphin, Swan River, Grandview)

Interlake-Eastern RHA: ☐ Interlake (e.g. Selkirk, Gimli, Stonewall, Arborg)

☐ North Eastman (e.g. Beausejour, Pine Falls)

Southern Health-Santé Sud: ☐ Central (e.g. Portage La Prairie, Winkler, Morden)

☐ South Eastman (e.g. Steinbach, Ste. Anne)

Q32. Are you:
- ☐ Male
- ☐ Female

Thank you for taking the time to complete the questionnaire.
Please return the completed questionnaire using the pre-paid envelope.

If you wish to <u>enter the draw for an iPad</u>, please provide an email address so that we can contact you if you win. This email contact will be removed from the survey document and will never be linked to the survey.

Email: _____

Appendix C: Chart Review Data Collection Sheet

Participant Unique Code Number: _____

<u>Data Collection Sheet: GDM</u>

(To be used with Master List)

<u>Protocol Title: Calcium and vitamin D in diabetes in pregnancy: Maternal and neonatal outcomes</u>

Data to be collected on paper: Yes ☐   No ☐

Data to be entered directly into computer spread sheet: Yes ☐   No ☐

<u>Data Elements to be collected</u>:

Demographic data and identifiers:

<u>From Inpatient Demographics Sheet:</u>

City/Town/Municipality: _____

First three digits of postal code: _____

Date of birth: (D/M/Y): _____/_____/_____

<u>Data elements from chart or database:</u>

<u>From Manitoba Prenatal Record/Laboratory Results:</u>

Infection Screening:

    <u>1.</u> Chlamydia: Yes ☐   No ☐   N/A ☐   Blood collection date (D/M/Y): _____/_____/_____

    <u>2.</u> Gonorrhea: Yes ☐   No ☐   N/A ☐   Blood collection date (D/M/Y): _____/_____/_____

    <u>3.</u> Trichomoniasis: Yes ☐   No ☐   N/A ☐   Blood collection date (D/M/Y): _____/_____/_____

    <u>4.</u> Group B streptococcus: Yes ☐   No ☐   N/A ☐   Blood collection date (D/M/Y): _____/_____/____

    <u>5.</u> Bacterial vaginosis: Yes ☐   No ☐   N/A ☐   Blood collection date (D/M/Y): _____/_____/_____

<u>From ACF Note/Obstetrical Triage Assessment Record:</u>

    Weight (kg) at end of pregnancy: _____   Gestational age (weeks): _____

Date completed (D/M/Y): _____/_____/_____

<u>From Birth Summary Part 1, 2, 3/Newborn Nursing Database:</u>

Gravida: _____   Para: _____

Gestational age (weeks) at delivery: _____   Date of infant birth (D/M/Y): _____/_____/_____

Fetal Loss: ☐ NO

☐ YES ☐ Spontaneous miscarriage (< 20 weeks gestation)

☐ Intrauterine fetal demise (> 20 weeks gestation)

Maternal Complications:

GDM management: ☐ Diet ☐ Insulin ☐ Oral Medications: _____

Smoking: Yes ☐ No ☐ N/A ☐

Substance abuse: Yes ☐ No ☐ N/A ☐

Alcohol abuse: Yes ☐ No ☐ N/A ☐

Anemia: Yes ☐ No ☐ N/A ☐

Hypertension: ☐ NO

☐ YES ☐ Gestational ☐ With protein ☐ No protein
☐ Pre-existing (chronic)

Singleton ☐ Multiple: ☐ A ☐ B ☐ C

Mode of delivery:

☐ Spontaneous vaginal delivery ☐ Induction

☐ C-section ☐ Elective ☐ Emergency

Reason for induction: _____ ☐ N/A

Reason for emergency C-section: _____ ☐ N/A

Reason for preterm labour: _____ ☐ N/A

Infant weight (g): _____

Apgar score: 1 min _____ 5 min _____ ☐ N/A

Incidence of shoulder dystocia: Yes ☐ No ☐ N/A ☐

NICU admission Yes ☐ No ☐

Reason for NICU admission: _____

From Prenatal Flow Sheet:

Eligible for Vitamin D (100,000 IU): Yes ☐ No ☐

1. Prior to 12 weeks gestation: Yes ☐ No ☐ N/A ☐ Date completed
(D/M/Y):_____/_____/_____

2. At 29-38 weeks gestation: Yes ☐ No ☐ N/A ☐ Date completed
(D/M/Y):_____/_____/_____

*POSTPARTUM DATA***:**

No return visit ☐   No show ☐   N/A ☐

Date of postpartum visit (D/M/Y): _____/_____/_____

Weight (kg): _____   N/A ☐

Blood pressure (systolic/diastolic mmHg): _____/_____   N/A ☐

OGTT (PG) results (mmol/L):

75 g   Fasting PG: _____   1 hr PG: _____   2 hr PG: _____   N/A ☐

Date of blood collection for OGTT (D/M/Y): _____/_____/_____   N/A ☐

Estimated weeks postpartum birth for OGTT: _____   N/A ☐

Postpartum HbA1c result (if available): _____   N/A ☐

Date of blood collection for HbA1c (D/M/Y): _____/_____/_____   N/A ☐

Estimated weeks postpartum birth for HbA1c: _____   N/A ☐

Diagnosis of T2DM postpartum: NO ☐   YES   ☐

Postpartum [25-OHD] (if available): _____   N/A ☐

Date of blood collection for [25-OHD] (D/M/Y): _____/_____/_____   N/A ☐

Season of blood draw for [25-OHD]:

☐ Spring (March - May)   ☐ Summer (June - August)

☐ Autumn (September - November)   ☐ Winter (December - February)

Estimated weeks postpartum birth for [25-OHD]: _____   N/A ☐

INITIAL VISIT DATA:

Date of initial visit (D/M/Y): _____/_____/_____

Height (cm): _____ Weight (kg): _____ BMI: _____ Date (D/M/Y): ____/____/____   N/A ☐

Gestational age (weeks): _____ Age (yrs): _____

Blood pressure (systolic/diastolic mmHg): _____/_____   N/A ☐

OGTT (PG) results (mmol/L):

50 g   1 hr PG: _____   N/A ☐

75 g   Fasting PG: _____   1 hr PG: _____   2 hr PG: _____   N/A ☐

Date of blood collection for 50 g OGTT (D/M/Y): _____/_____/_____   N/A ☐

Date of blood collection for 75 g OGTT (D/M/Y): _____/_____/_____   N/A ☐

HbA1c result (if available): _____   N/A ☐

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Date of blood collection for HbA1c (D/M/Y): _____/_____/_____   N/A ☐

Estimated gestational age (weeks) at blood collection OGTT/HbA1c: _____/_____

Serum [25-OHD] (nmol/L): _____

Date of blood collection for [25-OHD] (D/M/Y): _____/_____/_____

Season of blood draw for [25-OHD]:

☐ Spring (March - May)   ☐ Summer (June - August)

☐ Autumn (September - November)   ☐ Winter (December - February)

Estimated gestational age (weeks) at blood collection for [25-OHD]: _____

Prescription for vitamin D deficiency prescribed:

Yes ☐ No ☐ N/A ☐

Amount: _____

Date of prescription (D/M/Y): _____/_____/_____   ☐ N/A

Date prescription filled (D/M/Y): _____/_____/_____   ☐ N/A

Self-reported compliance of vitamin D treatment:

Yes ☐ No ☐ N/A ☐   Amount: _____

Date (D/M/Y): _____/_____/_____   ☐ N/A

From Dietitian Note:

Date of initial visit (D/M/Y): _____/_____/_____   ☐ N/A

         Self-reported lactose intolerance: ☐ N/A   ☐ NO   ☐ YES

Prenatal vitamin supplement: ☐ N/A   ☐ NO   ☐ YES   Brand: _____

Calcium supplement: ☐ N/A   ☐ NO   ☐ YES   Type: _____

                                                    Amount: _____

Vitamin D supplement: ☐ N/A   ☐ NO   ☐ YES   Type: _____

                                                    Amount: _____

Estimated dietary calcium intake (mg) (food only): _____

☐ <300   ☐ 300-600   ☐ 600-900   ☐ >900

Estimated dietary vitamin D (IU) (food only): _____

☐ <100   ☐ 100-200   ☐ 200-300   ☐ >300

Comments:

_____

_____

_____

_____

Data collected by (printed name and signature): _____

Date Data collected: _____

Appendix D: Master List for Data Collection

Master List

(The master list will be locked in a separate cabinet from the Data Collection/Capture Sheet)

Protocol Title: Calcium and vitamin D in diabetes in pregnancy: Maternal and neonatal outcomes

Hospital MRN #	Participant Code
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