University of Alberta

Use of Natural Health Products among pregnant women in Alberta: A preliminary analysis of the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort

by

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Abstract

Natural Health Products (NHPs) contribute to micronutrient intake during pregnancy. Results of this study revealed that >90% of the participants reported using ≥1 NHP in each trimester of pregnancy leading to high intakes of some micronutrients. Median daily reported intakes were 1000 mcg of folic acid, 400 IU of vitamin D, 250 mg of calcium and 27 mg of iron in each trimester of pregnancy. Compliance with IOM supplementation guidelines was high for folic acid (> 90%), vitamin D (> 67%) and calcium (>78%) but lower compliance was observed in iron (<30%) and when all four nutrients were analyzed (<15%). Significant differences were observed between level of education ($p = 0.049$) and ethnicity background ($p = 0.048$) of participants that followed supplementation guidelines compared to those who did not. Intake of NHPs contributed significantly to meeting micronutrient requirements in pregnancy.

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List of Symbols and Abbreviations

$\bar{x}$	Mean
AHA	arachidonic acid
ANOVA	analysis of variance
APrON	Alberta Pregnancy Outcomes and Nutrition
BMI	body mass index
CI	confidence interval
DHA	docosahexanoic acid
DFE	dietary folate equivalents
DIN	drug identification number
DRIs	dietary reference intakes
EAR	estimated average requirement
EFAs	essential fatty acids
EPA	eicosapentaenoic acid
FAO	Food and Agriculture Organization
FFQ	food frequency questionnaire
hCG	human chorionic gonadotropin
IDA	iron deficiency anemia
IOM	Institute of Medicine
IU	international units
Kcal	kilocalories
NHPD	Natural Health Product Directorate
NHPs	Natural Health Products
NPN	Natural Product Number

NTDs	neural tube defects
NVP	nausea and vomiting of pregnancy
OR	odds ratio
RDA	recommended dietary allowance
RR	relative risk
SD	standard deviation
SIQ	Supplement Intake Questionnaire
UL	upper limit
UN	United Nations
UNU	United Nations University
WHO	World Health Organization

CHAPTER I

I.1 Introduction

Pregnancy has been described as a hyperdynamic, hypermetabolic and hypervolemic state in which a higher workload on the heart secondary to an increased blood volume, and an increased metabolic rate are present (Torgersen, et al., 2006). During pregnancy, the human body undergoes a wide range of changes from the moment of conception. Anatomical, physiological and biochemical adaptations occur in order to support the growth and development of the fetus (Williamson, 2006).

To sustain the changes taking place, nutrient requirements, as well as it intestinal absorption increase, while nutrient excretion through the kidney or gastrointestinal tract is reduced (King, 2000). Throughout pregnancy, nutrients: (1) adhere to new tissues or are deposited in maternal stores, (2) redistribute among tissues or (3) increase their metabolic rate (King, 2000). Hormonal changes, fetal demands and maternal nutrient supply are important factors involved in nutrient metabolism and are necessary to consider for nutrient requirements in pregnancy. According to the 1985 FAO/WHO/ ONU report, energy requirements during pregnancy should be met by an adequate food intake that will balance a woman's energy expenditure, assuming a healthy body weight and body composition and desirable physical activity. Energy intake that meets energy needs is associated with an optimal pregnancy outcome (WHO, 1985). Optimal maternal nutritional status before and during pregnancy is a determinant of healthy growth and development

of the fetus, as well as being an important factor for overall maternal health (Butte et al., 2005).

Inadequate maternal nutritional status has been associated with restricted placental and fetal growth in animal and human models (Bell, 2002; Wu, et al., 2004). In addition, an inadequate maternal nutritional status has been suggested to be one of the main risk factors for maternal mortality and has been associated with degenerative diseases of the offspring, such as coronary heart disease, hypertension, type 2 diabetes and insulin resistance (Barker, 2003). Whenever nutritional needs exceed intake, fetal growth and development are impaired as the fetus is most vulnerable to the effects of a poor maternal diet; especially for the first weeks of development which occur before pregnancy is confirmed (Williamson, 2006). Requirements for many micronutrients also increase; B-vitamins, vitamin D, calcium and iron play important roles in maintaining maternal health and providing the fetus with the necessary nutrients for optimal development (Carlson et al., 2007). These key nutrients will be the specific focus of this thesis.

Deficiencies of such nutrients have been previously reported and positively related to detrimental conditions in both the mother and the offspring (Casanueva et al., 2003; Allen, 2005; Haider et al., 2006; Goh et al., 2006; De Wals et al., 2007). Conclusive evidence of the importance of folic acid intake, an important B vitamin, in the prevention of Neural Tube Defects (NTDs) has been extensively documented (MRC Vitamin Study Research Group, 1991; Czeizel, et al., 1992; Lumley, et al., 2006) in response to the recognition, folic acid fortification of most

cereal grain products in Canada began in 1998 (Ray, et al., 2002; French et al., 2003). Fetal bone mineral accretion is strongly affected by maternal vitamin D status (Ward, et al., 2007) and severe maternal deficiency can lead to neonatal rickets and osteomalacia (Ward, 2005). Poor vitamin D status has been diagnosed among Canadian pregnant women and it is further related to smaller size of the newborn, dental malformations and decreased vitamin D concentrations in breast milk (Ward, 2005; Weiler, et al., 2007). In addition to vitamin D, calcium is also involved in skeletal formation, with the greatest period for fetal calcium accretion occurring during the third trimester (Prentice, 2003). One study reported that maternal calcium intake as well as cord blood calcium were positively associated with the child's bone mass in early childhood (Tobias, et al., 2004). Iron deficiency during pregnancy is the main cause of anemia and it is related to an increased risk of maternal mortality and low birth weight, secondary to preterm birth (Allen, 2000). Iron deficiency anemia (IDA) is considered a public health concern in many developing countries where approximately 52% of pregnant women develop this condition (WHO/UNICEF/UNU, 2001). While presenting with a lower prevalence, iron deficiency anemia is also observed in developed countries (WHO/UNICEF/UNU, 2001). It is important to mention that there are other nutrients which play an important role during pregnancy. Dietary intakes of arachidonic acid (AHA), docosahexaenoic acid (DHA), iodine, choline and zinc may also be deficient in this population. As a result, there is a concern that women may not meet the nutritional requirements in pregnancy solely from food sources and guidelines promoting the use of Natural Health Products (NHPs) have been

released by different institutions to try to prevent deficiencies or to improve intake (Wilson, et al., 2007; Health Canada 2009).

I.2 Rationale

With the understanding of the roles that folic acid, vitamin D, calcium and iron play in maintaining optimal maternal nutrition status and fetal development, there have been widespread attempts to improve intake of these micronutrients in women of child-bearing age. Food fortification of cereal grains with folic acid has been mandatory in Canada since 1998 providing approximately 0.1 – 0.2 mg of additional folic acid per day (Ray, 2004). Food products fortified with vitamin D include fluid milk (176 IU per 250 ml serving) and margarine (530 IU/100 g) (Health Canada, 2003). Calcium has also been included in plant-based beverages and orange juice, as well as 110 mg of added calcium per 100 grams in corn meal (Health Canada 2001; Department of Health 2006). Iron is also added to corn meal in quantities between 2.9 and 5.7 mg per 100 grams, and in breakfast cereals and bread with 4 and 9 milligrams per portion (Health Canada 2003; Health Canada 2005). Despite these strategies, Canadian women may fail to meet nutrient recommendations for the prenatal period. Pick and others analyzed micronutrient content of the diet of 52 Canadian pregnant women in an urban setting, demonstrating that women failed to meet dietary intakes of folic acid (mean intake of 331±12.2 mcg/day) and iron (mean intake of 15.9 ± 0.58 mg/day) (Pick et al., 2005). In a study by Berti and others with Canadian women living in the Arctic, similar findings were observed. These pregnant women had inadequate intakes of folic acid whereby almost 90% of them were not meeting the Estimated Average Requirement (EAR) and up to 84% of pregnant women were not meeting the EAR for iron (Berti et al., 2008). To prevent micronutrient deficiencies to

occur in pregnancy the use of NHPs has been recommended (IOM 2008; Health Canada 2009). Health Canada, under the Natural Health Products Regulations which have been in effect since 2004, defines NHPs as (Canada Gazette, 2003):

a. Single and multi-vitamin and mineral supplements

b. Herbal remedies

c. Homeopathic medicines

d. Traditional medicines such as traditional Chinese medicines

e. Probiotics, and

f. Other nutrients such as amino acids and essential fatty acids

Recent data suggest that the use of NHPs is increasing. A survey was carried out among 2,004 Canadian adults, to assess attitudes, awareness and use of NHPs (NHPD, 2005). Results demonstrated that the majority of people agree that NHPs can be used to promote health (77%) or treat illness (68%) and up to 71% of respondents reported some use of NHPs. These findings are consistent with other nutritional surveys done worldwide (National Center for Health Statistic, 2000; Radimer, et al., 2004; Nutrition Business Journal, 2006). In Canada, prevalence of NHP use is highest among residents in Alberta (74%), specifically with those having a higher level of academic attainment, higher annual income, and between 18 and 34 years of age (76%). Women (78%) were more likely than men (64%) to use NHPs (NHPD, 2005).

Data regarding the type, frequency and dose of NHPs used by pregnant women is limited. Describing the reported intake of NHPs by this group will increase the knowledge of the extent to which NHPs are used to meet the recommendations for key micronutrients, as well as describing the characteristics of users who report regular consumption during the gestational period.

Different sets of guidelines have been developed targeting the need for micronutrient supplementation before and during pregnancy, but compliance with them has not always been successful. This is in part, due to nausea and vomiting of pregnancy (NVP) (Koren et al., 2006), lack of knowledge (Ray, et al., 2004), unplanned pregnancies (Morin, et al., 2002), socio-economic status and level of education (Millar, 2004).

In 2009, Health Canada stated in its Prenatal Nutrition Guidelines for Health Professionals (Health Canada, 2009), that in addition to eating according to Canada's Food Guide, women of childbearing age should consume a daily multivitamin containing 400 mcg of folic acid for a minimum of three months before pregnancy and continuing throughout gestation. The Institute of Medicine (IOM) in its Dietary Reference Intakes for folate, states that a Recommended Dietary Allowance (RDA) of 600 mcg per day of dietary folate equivalents (DFEs) is required in order to maintain normal folate status in pregnant women (IOM,2008). This recommendation does not distinguish dietary folate intake from folic acid supplements as Health Canada's guideline does; therefore they have adjusted this by making a higher recommendation.

Vitamin D and calcium status during pregnancy may affect skeletal development of the newborn (Prentice, 2003; Javaid, et al,. 2006), yet there is no conclusive evidence of the need for vitamin D or calcium supplementation in pregnant women. Health Canada and the IOM's current recommended dietary allowance (RDA) for women from 19 to 50 years of age, including pregnant women, is a daily intake of 600 IU of vitamin D (Health Canada 2010; IOM 2010) and 1000 mg/day of calcium. If pregnancy occurs before 18 years of age, the calcium recommendation increases to 1300 mg/day (IOM, 2010).

For iron, Health Canada also emphasizes the need for supplementation during pregnancy as the average intake of this mineral (~15 mg/d) among pregnant women is below the recommended amount (27 mg/d) (Unpublished, Canadian Community Survey, 2004). According to Health Canada, iron supplements should provide between 16 to 20 mg of iron per daily dose (Health Canada, 2009). The IOM established the RDA for iron as 27 mg per day to build iron stores during the first trimester of pregnancy and established iron supplementation at 30 mg of elemental iron/day for non anemic pregnant women during the second and third trimester (IOM, 1992).

Natural Health Products may contribute to achieving desired levels for folic acid, vitamin D, calcium, and iron, as well as other micronutrients. It is important to consider that NHPs are over-the-counter products and do not require a prescription to be sold. This unregulated availability could lead to high intakes and possible toxic effects that could affect the health of the mother and/or the fetus. This thesis describes the use of the NHPs among a cohort of pregnant

women in Alberta. As vitamin/mineral supplements contribute to meeting nutritional requirements, four specific micronutrients important in pregnancy and which have been reported with inadequate intake in pregnant women were examined more closely - folic acid, vitamin D, calcium and iron. In addition, the majority of prenatal NHPs contain these key micronutrients in their formulations. Thus, it was important to determine to what extent NHPs contributed to meeting overall nutritional recommendations for pregnant women. Finally it was determined whether pregnant women were using NHPs in amounts consistent with Health Canada's Prenatal Nutrition Guidelines and the IOM recommendations.

I.3 Overall Purpose

The overall purpose of this thesis was to increase the knowledge and understanding of NHPs by assessing the use of these products by pregnant women in Alberta, by describing the type and frequency of NHPs consumed, and also by identifying possible safety concerns based on reported intakes.

A second aim was to determine if current guidelines for folic acid, vitamin D, calcium and iron supplementation were being followed by a cohort of pregnant women in Alberta.

I.4 Research Questions

a. What products and daily intake of NHPs were reported by women enrolled in the Alberta Pregnancy Outcomes and Nutrition (APrON) study during their pregnancies?*

    i. Did the use of NHPs vary between trimesters of pregnancy?

b. In a sub-group of key micronutrients required during pregnancy (folic acid, vitamin D, calcium and iron), what proportion of the recommended dietary intake was met through the use of NHPs?

    i. Did the intake of folic acid, vitamin D, calcium and iron from NHPs vary between trimesters of pregnancy?

c. Were women enrolled in the APrON study meeting the established supplementation guidelines (Health Canada/Institute of Medicine) for folic acid, vitamin D, calcium and iron during pregnancy?

    i. What are the characteristics of the pregnant women who met the supplementation guidelines, compared to those who did not?

    ii. Were there potential safety concerns regarding the type (herbal preparations) and dose (intakes above the Upper Limit) of NHPs reported by pregnant women enrolled in the APrON Study?

** Note: this study represents the first 600 women from the APrON study only; not the entire cohort.*

I.5 Objectives of the research were:

a. To develop a questionnaire to assess the type, dose and frequency of use of NHPs consumed by the APrON study participants throughout their pregnancies.

b. To develop a database of all NHPs consumed by the APrON study participants throughout their pregnancies.

c. To examine what proportion of the dietary recommendations for pregnancy for folic acid, vitamin D, calcium and iron were met through the use of NHPs.

d. To determine if current Health Canada and Institute of Medicine guidelines regarding folic acid and iron supplementation, in addition to recommended intakes of vitamin D and calcium were being met by the APrON study participants.

e. To identify safety concerns regarding improper use of NHPs consumed during pregnancy.

CHAPTER II LITERATURE REVIEW

II.1 Introduction

Pregnancy requires an increased intake of several nutrients to support maternal physiological adaptations as well as fetal growth and development. Nutrient intake in the periconception period and during gestation has been identified as one determining factor for maintaining maternal health and promoting fetal growth and development, as the fetus is sensitive to the availability of nutrients from the moment of implantation.

Maternal nutrient stores and dietary intake are responsible for meeting fetal demands, especially for certain essential micronutrients required for an optimal outcome. Folic acid, vitamin D, calcium and iron play a very important role during the prenatal period and they are the main focus of this thesis. Several studies have reported an inadequate nutrient intake in the obstetric population in both developing and industrialized countries; and as a result, there is an increased risk of maternal morbidity and mortality in addition to an increased risk of congenital defects.

In order to increase micronutrient intakes and prevent nutrient deficiency-related congenital defects from occurring, the use of Natural Health Products (NHPs) has been recommended by health organizations including the Institute of Medicine (IOM) in the United States and Health Canada, Government of Canada. However, the extent to which such products are used by pregnant women during the course of their pregnancies has not been well documented.

II.2 Physiology of pregnancy

Pregnancy is a dynamic state characterized by the presence of several anatomic, metabolic and hormonal adaptations to support the growth of maternal tissues as well as the growth and development of the fetus (Williamson, 2006). Such changes dramatically impact body composition, metabolic rate, cardiac output and hormonal response of pregnant women throughout the gestational period. The first half of pregnancy is usually described as a period in which the body prepares for the exponential growth of the fetus which occurs in the later stages of gestation (King, 2000). It is also the period when many anatomical and hormonal changes take place. The second half of pregnancy is distinguished by an increase in nutrient demand, secondary to the needs of the fetus. As a result, basal metabolism, energy expenditure and nutrient stores are affected (King, 2000). Some of the most significant adaptations are described below.

a. Blood Volume

Blood volume increases between two to three litres during the sixth week of pregnancy (Bernstein, et al., 2001) allowing an appropriate delivery of oxygen to various maternal tissues such as the uterus and the placenta, in addition to the developing fetus (Torgersen, et al., 2006). Almost half of this volume increase occurs in the plasma, while approximately fifteen to twenty percent appears in the form of red cell mass (Picciano, 2003). The low increase of red cell mass relative to the plasma results in low values of haemoglobin and hematocrit leading to a condition known as "physiologic anemia" (Sifakis, 2000) which must be carefully

monitored to detect the development of iron deficiency anemia (IDA) during pregnancy (IOM, 1993).

b. Cardiac Output

Secondary to the hemodynamic changes (blood volume, blood pressure, heart rate and blood flow distribution) in pregnancy, a greater workload on the heart is observed (Torgersen, et al., 2006). Cardiac output is defined as the amount of blood that is pumped by the heart per unit time (L/min) (Spaanderman, 2000). In early stages of pregnancy it increases by one litre per minute and may reach up to seven litres per minute during the third trimester (Torgersen, et al., 2006). Cardiac output has been described as the most significant haematic adaptation occurring during gestation (Blackburn, et al., 2006).

c. Endocrine Changes

Hormones play an important role in pregnancy from the moment of implantation until after delivery when lactation takes place. Several hormones influence the growth rate of the fetus and maternal tissues, nutrient transport and other essential functions (Norwitz, et al., 2001). Information on the synthesis, metabolism and functions of pregnancy hormones is extensive and has been reviewed in detail elsewhere (Norwitz, et al., 2001; Kodaman & Taylor, 2004).

The release of hormones begins shortly after fertilization. An increase of human chorionic gonadotropin (hCG) in the plasma occurs after implantation (Picciano, 2003; Weissgerber, et al., 2006). Adequate levels of hCG support the function of the corpus luteum which provides progesterone and estrogen during early stages of gestation (Kallen, 2004). After the corpus luteum degrades, the placenta

becomes responsible for the synthesis of steroid hormones for the remaining time (Picciano, 2003). Synthesis of estrogen and progesterone depends on maternal and fetal precursors (Weissgerber, et al., 2006). Both, progesterone and estrogen, aid in the maintenance of the uterine environment and the further development of the placenta (Picciano, 2003). The roles of progesterone are diverse, from stimulating maternal respiration to relaxing smooth muscle (mainly the uterus and gastrointestinal tract) (Di Renzo, et al., 2005). It is also responsible for inhibiting milk secretion during pregnancy and promoting breast lobular development (Di Renzo, et al., 2005). Secretion of estrogen increases as pregnancy evolves, improving uterine growth and promoting uterine blood flow; it is also involved in breast development. Estrogen precursors, synthesized primarily in the fetus, become a reliable measurement for fetal viability (Hytten and Leitch, 1971).

d. Weight Gain

Weight gain during pregnancy is comprised of several components including: the fetus, amniotic fluids, the placenta, blood supply, extracellular fluids, enlargement of the uterus and mammary glands and finally the increase in maternal fat stores (Picciano, 2003). An adequate maternal weight gain has been related to optimal pregnancy outcomes (Abrams, et al., 2000). Risk of developing complications during pregnancy, labour or delivery can be diminished with an appropriate weight gain (Butte, et al., 2005).

In 2009, the IOM released new guidelines to define an optimal range for weight gain during pregnancy, in which pre-pregnancy weight is considered the main factor which determines individual requirements (Rasmussen, et al., 2009). Health

Canada's recommendations for total weight gain during pregnancy follow the same guidelines as the ones currently used by the IOM (Health Canada, 2009). Table 1 shows current recommendations for gestational weight gain based on pre-pregnancy body mass index (BMI). An ideal scenario to enter pregnancy would portray a woman with a body size and body composition in the normal ranges, (Andreasen, et al., 2004) shown below.

TABLE 1. Institute of Medicine recommendations for total and rate of weight gain during pregnancy.

Pre-pregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range (kg)	Range (lbs)	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m^2)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m^2)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m^2)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥30.0 kg/m^2)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

*Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (Rasmussen, et al., 2009).

II.3 Nutrition for the gestational period

a. Nutrient requirements during pregnancy

Maternal nutritional status is the principal factor affecting the growth and development of the fetus and it should be carefully observed. Several studies have shown that maternal nutritional status at the time of conception is closely related to maternal and fetal outcomes (Williamson, 2006; Abu-Saad, et al., 2010). Nutrient requirements increase not only to provide the fetus with an optimal

environment, but also to support the growth of maternal tissues during pregnancy and lactation (Picciano, 2003). The embryo is most vulnerable to maternal dietary intake so it is important that nutrient requirements meet the needs of the mother (Abu-Saad, et al., 2010), establish maternal nutrient stores that will aid in the development of the fetus and provide the embryo with the essential nutrients for its development (Williamson, 2006). Failure to meet nutrient requirements could result in intrauterine growth retardation or low birth weight, as well as other maternal complications such as iron deficiency anemia (Abu-Saad, 2010). The increased demand for some nutrients during the gestational period can be as high as ~50% compared to nutrient requirements of non pregnant women; protein, iron and folic acid are some examples (Carlson, et al., 2007).

As previously discussed, pregnancy is responsible for many physiological adaptations to support gestation. Adjustments in metabolism also take place in order to improve the utilisation and absorption of nutrients (Williamson, 2006). Those adjustments occur as a result of hormonal changes, fetal demands and maternal nutrient supply (King, 2000). There are several ways in which nutrient metabolism adapts to meet the demands of pregnancy. Nutrients can be deposited in maternal stores, redistributed among maternal tissues, have increased absorption due to homeostatic responses, have decreased urinary excretion, or simply have a more efficient utilisation (Williamson, 2006). Iron, calcium, copper and zinc have an increased absorption while urinary excretion of riboflavin is reduced during the prenatal period (Williamson, 2006).

i. Energy

The total energy cost of pregnancy has been estimated to be approximately 77,000 kcal (FAO/WHO/UNU, 2004). Energy requirements increase during pregnancy in order to meet the needs to deliver a full-term, healthy infant of satisfactory size and body composition (Goldberg, 2002). Additional energy intake is necessary for the growth and preservation of the fetus and maternal tissues i.e. the placenta; however energy requirements only increase during the 2nd and 3rd trimester by 340 and 450 kcal/day respectively (IOM, 2002). Energy metabolism changes throughout each trimester and varies between individuals (IOM 2005; Forsum, et al., 2007; Mehta, 2008); therefore recommendations must consider each woman's BMI, age, appetite and physical activity (Giroux, et al., 2006).

ii. Protein

During gestation, protein is deposited in fetal and maternal tissues at a rate that increases as pregnancy progresses (IOM, 2002). It has been estimated that approximately 21 grams of protein are deposited daily (Picciano, 2003; Williamson, 2006). Studies where protein intake was assessed around the time of conception and during early stages of pregnancy, demonstrated that an adequate maternal protein intake was positively associated with birth weight (Moore, et al., 2004; Cucó, et al., 2006; Olsen, et al., 2007). The current DRI states that pregnant women should consume a minimum of 70 grams of protein per day in order to meet current recommendations and support the development of maternal tissues such as the uterus and the placenta (IOM, 2002; Abu-Saad, et al., 2010).

iii. Fat

Pregnancy is a critical period where essential fatty acids and their longer-chain derivatives play an important role in the development of the brain and nervous system of the fetus (Williamson, 2006). A high intake of long-chain omega 3 fatty acids during pregnancy has been shown to affect pregnancy outcomes by increasing fetal growth (Allen, et al., 2001; van Eijsden, et al., 2008). Adequate dietary intakes of docosahexaenoic acid (DHA) during pregnancy increases the supply to the fetus and positively influences visual acuity, cognitive function and maturity of sleep patterns in the infant after birth (Hadders-Algra, et al., 2007).

iv. Carbohydrates

Carbohydrates are the main source of energy for the fetus (Stein et al. 2003), which uses maternal glucose for fetal brain function. Current recommendations of 175 grams per day, considers both maternal and fetal glucose needs (IOM, 2002).

v. Vitamins and minerals

With the understanding that pregnancy involves several biochemical changes, it is important to acknowledge the role that vitamins and minerals play during gestation. There are some micronutrients of special concern in this period as there is a greater potential for deficient intake. These include: folic acid, vitamin D, calcium and iron (Giroux, et al., 2006) and they will be discussed later in this chapter. A more detailed review of recommended intakes of the remaining micronutrients has been published by the IOM (IOM, 2002). Table 2 summarizes the requirements for key nutrients during pregnancy.

Table 2. Dietary reference intake (DRI) for macronutrients and micronutrients during gestation.

Age group (y)	Protein (g/d)	Linoleic acid (g/d)	A-linolenic acid (g/d)	Carbohydrate (g/d)	Folic Acid (mcg/d)	Vitamin D (IU/d)	Calcium (mg/d)	Iron (mg/d)
14 - 18	71	13*	1.4*	175	600	600	1,300	27
19 - 30	71	13*	1.4*	175	600	600	1000	27
31 - 50	71	13*	1.4*	175	600	600	1000	27

Adapted from the Institute of Medicine DRI reports. Values shown as Recommended Dietary Allowances (RDAs) unless followed by (*) which indicates Adequate Intakes (AIs). (IOM,2002;IOM 2010).

II.4 Dietary intakes of pregnant women

Nutritional status of the pregnant population has been identified as a potential risk factor that could compromise maternal and fetal health in several developing countries; nevertheless inadequacy of intake is not uncommon in industrialised countries where high-energy diets do not always reflect nutrient dense diets (Mathews, 1999; Bodnar et al., 2002). Studies worldwide have assessed dietary intake of pregnant women in different stages of gestation in order to have a better understanding of its influence on birth outcomes. Rifas-Shiman and others assessed dietary intakes of 1543 women in the United States to compare nutrient intake between the first and the second trimester of gestation (Rifas-Shiman, et al., 2006). Participants were asked to report food intake in two different gestational time points using a Food Frequency Questionnaire (FFQ). Overall mean food intake was not significantly different between trimesters however, a moderate change in individual food intake from the first to the second trimester was observed, resulting in an increase in vitamin D intake of ~7% during the second trimester when compared to the first. When considering dietary and

supplementary sources of micronutrients, folate and iron increased by 31 and 45% respectively from the first to the second trimester (Rifas-Shiman, et al., 2006). Pinto and colleagues (Pinto, et al., 2008) assessed the maternal diet of 249 women in Portugal prior to conception and during pregnancy with a FFQ. Despite and increased dietary intake of vitamin A, vitamin E, riboflavin, folate, calcium and magnesium during gestation, the prevalence of inadequate intakes remained high for folic acid and iron with 91% and 88% respectively being affected (Pinto, et al., 2008). A Finnish study assessed the diet of 797 women during their pregnancies, also using a FFQ (Arkkola, et al., 2006). Results in this study showed that most of the participants used nutrient supplements during their pregnancies, with iron (78%), vitamin D (40%) and folic acid (39%) supplements being the most commonly consumed. Regardless of the use of dietary supplements, 44% of the women had folic acid intakes below recommendations and up to 85% had inadequate intake of vitamin D (Arkkola, et al., 2006).

II.5 The role of supplements

a. Are supplements needed?

Maternal undernutrition is becoming an important public health issue worldwide as there is growing evidence of the inadequacy of dietary intakes among pregnant women (Bhutta, et al., 2009). Dietary intake of micronutrients can be marginal during pregnancy to the point that some pregnant women can become clinically deficient (Allen, 2005). Several strategies have been implemented to reduce nutrient deficiencies globally; food fortification and the recommendation for supplements are some examples. Despite these efforts women of reproductive age

continue to have inadequate intakes of important nutrients (Allen, 2005). Micronutrient deficiency in developed countries is associated with low maternal age, poverty, and inadequate diets (Bhutta, et al., 2009). Ideally, micronutrient deficiencies should be prevented or treated before a woman becomes pregnant (Allen, 2005). To prevent such deficiencies it has been recommended that pregnant women consume a multivitamin and mineral supplement. This recommendation extends to all women of reproductive age, as the risk of having an unplanned pregnancy is high (Health Canada, 2009). The effectiveness of this practice in well nourished populations has been questioned, as beneficial effects have only been documented for folic acid and iron supplementation in the prevention of neural tube defects (NTDs) and anemia respectively (MRC Vitamin Study Research Group 1991). However, multiple micronutrient supplementation has shown a protective effect in other birth outcomes. Goh, et al completed a meta-analysis that evaluated the use of multivitamins before conception and their use throughout the first trimester of pregnancy, resulting in a decrease in birth defects, including defects of the neural tube (Goh, et al., 2006). Results suggested a protective effect against NTDs when supplements were taken prior to conception (odds ratio [OR] 0.67, 95% confidence interval [CI] 0.58-0.77 in case control studies, and an OR of 0.52, 95% CI 0.39-0.69 in cohort and randomized controlled studies); against cardiovascular defects (OR 0.78, 95% CI 0.67-0.92 in case control studies; OR 0.61, 95% CI 0.40-0.92 in cohort and randomized controlled studies); and against limb defects (OR 0.48, 95% CI 0.30-0.76 in case

control studies; OR 0.57, 95% CI 0.38-0.85 in cohort and randomized controlled studies) (Goh, et al., 2006).

Also from a meta-analysis, Shah and Ohlsson concluded that multivitamin and mineral supplements had a high impact on the decrease in low birth weight babies (those whose weight at birth is below 2.5 kilograms / 5.5 pounds). The use of a multivitamin was associated with a reduction of 17-19% of the risk of delivering a low birth weight baby, when compared to iron and folic acid supplements alone (Shah & Ohlsson, 2009). In addition, the mean birth weight of babies whose mothers consumed a multiple vitamin and mineral supplement was 54 grams higher (95% CI 36g-72g) when compared with those who consumed only iron-folic acid supplements (Shah & Ohlsson, 2009). Benefits on enhanced survival (Shankar, 2008) and growth (Vaidya, et al., 2008) have also been reported as a result of micronutrient supplementation. Botto and others completed a clinical trial in which results showed a protective effect of multivitamin use against NTDs, orofacial clefts and some heart defects (Botto, et al., 2002). Additionally, multiple micronutrient supplementation has been shown to significantly decrease the number of low birth weight babies (relative risk [RR] 0.83; 95% CI 0.76-0.91), small-for-gestational-age babies (length and head circumference $<10^{th}$ percentile for the corresponding gestational age) (Botto, et al., 2002) (RR 0.92; 95% CI 0.86-0.99) and maternal anemia (RR 0.61; 95% CI 0.51-0.71) when compared with two micronutrients or less, a placebo or no supplementation (Haider, et al., 2006).

Cogswell and others carried out an intervention study where 30 mg of iron were provided daily to pregnant women from their 20^{th} to their 28^{th} week of gestation to determine the prevalence of maternal anemia, birth weight, birth length and gestational age. When compared with placebo, iron supplementation had no effect on the prevalence of maternal anemia during the third trimester of pregnancy, however, an increased birth weight (+ 206 g) was observed and a decreased incidence of low birth weight infants (4% versus 17%) was reported (Cogswell, et al., 2003). These results suggest that iron supplementation during the second and third trimester of gestation could have a positive effect in countries where women present with low iron stores, such as Canada (Health Canada, 1999).

b. Natural Health Products (NHPs)

i. Definition and Classification

Health Canada's definition of a NHP refers to the function for which it is used and the substances it contains. The function of a NHP is described as being for the "diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state in humans; can be used for restoring, correcting or modifying the organic functions in humans in such a manner that maintains or promotes health" (Health Canada, 2003). The substance component is the "specific medicinal ingredients or combination of such that are permitted in a dosage form including a plant (or plant material), alga, bacterium, fungus, non-human animal material, vitamins, amino acids, essential fatty acids, minerals, probiotics or the synthetic form of any of the ingredients listed" (Health Canada, 2003). Products that are

considered to be NHPs, according to the definition (Health Canada, 2009) include:

- Vitamins – Essential substances, in small quantities, for the normal functioning of metabolism in the body; which cannot usually be synthesized in the body but occur naturally in certain foods.
- Minerals – An inorganic solid with a definite and predictable chemical composition and physical properties.
- Herbal remedies - A medication prepared from plants or plants material.
- Homeopathic medicines - Medicines that are manufactured from or contain as medicinal ingredients only those substances or sources referenced in the *Homeopathic Pharmacopoeia* of the United States, the *Homöopathische Arzneimittel*, the *Pharmacopée française* or the *European Pharmacopoeia*.
- Traditional medicines - The sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. Traditional medicine has a long history (50 consecutive years) of use.
- Probiotics - A monoculture or mixed-culture of live micro-organisms that benefit the microbiota indigenous to humans.
- Amino acids - A class of organic molecules containing amino and carboxylic groups, forming the chief constituents of proteins found in a

plant or a plant material, an alga, a bacterium, a fungus, or a non-human animal material.

- Essential fatty acids – A fatty acid that cannot be synthesized in the body; for this reason, it must be supplied through the diet or a supplement. Current knowledge indicates that there are only two essential fatty acids: linoleic acid and a-linolenic acid. All other fatty acids (such as oleic acid, conjugated linoleic acid, gamma-linoleic acid, arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid) are considered extracts or isolates

Regulations of NHPs were initiated on January 1, 2004 and apply to all NHPs on the market today (Health Canada, 2009). Products that have met Health Canada's NHP Regulations (Health Canada, 2010) are assigned a Natural Product Number (NPN) or a Drug Identification Number (DIN) consisting of an eight digit numerical code; meaning that such product has been assessed for its quality, safety and efficacy by Health Canada (Health Canada, 2010).

ii. Use of Natural Health Products by pregnant women

Recommendations regarding the use of certain NHPs by pregnant women, specifically vitamins and minerals, have become more common after the benefit of folic acid in preventing congenital effects was well documented as reviewed by Galbraith (Galbraith, 2004). However, as described previously, NHPs include a wide range of items, and usage by pregnant women is unclear. These preparations may be purchased without a medical prescription and therefore they can be easily accessed by pregnant women. Glover et al studied the intake of NHPs in a rural,

obstetric population with 578 participants in West Virginia, USA (Glover, 2003). Results showed that the use of NHPs was high; 92% of participants reported the intake of prenatal vitamins, 33% used single iron supplements, while only 3% reported the use of single folic acid supplements. Herbal remedies were also investigated, and approximately 45% of women reported the use of at least one herbal remedy (Glover, 2003). An Australian study assessed the intake of vitamins, minerals and herbal supplements of 211 women at an antenatal clinic (Maats, et al., 2002). The majority of women reported the use of a vitamin and mineral supplement in conjunction with a herbal supplement during their pregnancies; folate (70%), iron (33%) and multivitamin (27%) supplements were the NHPs most frequently reported (Maats, et al., 2002). In San Francisco, California, Tsui and colleagues examined the usage of NHPs in a pregnant population; 150 women were included in the study, and the authors found that only 13% reported the use of NHPs in the course of their pregnancies, including herbal remedies (Tsui, et al., 2001). An observational study by Refuerzo and others reported a high (97%) use of NHPs among 418 pregnant women in Michigan, USA. Prenatal supplements were most commonly used (85%), while single iron (42%) and folic acid supplements (5%) were reported less often. Of note, approximately 4% of women surveyed reported the intake of at least one herbal remedy (Refuerzo, et al., 2005). Use of NHPs in Hispanic pregnant women was observed by Bercaw and others (Bercaw, et al., 2010). Of the 500 women surveyed, ~77% took prenatal vitamins while only 21% reported a single

folic acid supplement. The use of herbs was also observed in this study with ~19% of women reporting their use (Bercaw, et al., 2010).

iii. Role of Natural Health Products in meeting current recommendations for key micronutrients.

As reported above, there are some studies which have described the use of different NHPs by groups of pregnant women, yet the contribution that these products make to overall nutrient requirements is rarely reported. Data collection on dietary supplement use has been described as challenging and time-consuming, but necessary to fully understand the closest estimation of micronutrient intake (Radimer, 2004).

A cohort study in Norway with approximately 40,000 pregnant women enrolled, did examine the use and contribution that NHPs make to the total micronutrient intake. Dietary intake was examined through a FFQ including a section on dietary supplements. After comparing total micronutrient intake with the Nordic Recommendations for pregnant women, it was observed that micronutrient intakes fell within the recommendations for the Norwegian population with the exception of vitamin D, folic acid, iron and iodine. The majority of the participants (81.4%) reported the use of one or more NHPs during the first 4-5 months of pregnancy (Haugen, et al., 2008). Of note, approximately 33% of supplement users reported more than three different products. Considering both sources of micronutrient intake, dietary and supplements, 45% of supplement users did not reach the recommended intake for vitamin D. However this percentage increased to 99% for women who did not use a dietary supplement. Folic acid was also primarily

obtained by the use of supplements, as 97% of nonusers failed to meet the recommended intake, but only 34% of supplement users could not meet the recommended intake. In this study, the use of supplements contributed to more than 50% of the total intake of vitamin D, DHA, eicosapentaenoic acid (EPA), vitamin B6, folic acid, copper and iron. Results from this study emphasize that the recommended dietary intake of these specific nutrients would unlikely be reached without supplementation (Haugen, et al., 2008). Similar reports were observed in a Finnish study where dietary supplements are recommended to assist in meeting the nutritional needs of the pregnant population (Arkkola, et al., 2006). Arkkola and colleagues examined the food choices and the intake of NHPs of 800 pregnant women. Diet was assessed with a FFQ while NHP information including brands, manufacturer, dose and frequency of use was reported. Vitamins, minerals and herbal products were considered. While the percentage of participants who met the recommended intake for vegetables and fruits was low (30%), the majority of the women (85%) reported the use of some kind of NHP to complement their diet. Iron, vitamin D and folic acid were primarily obtained through the use of NHPs, which provided approximately 80% of the vitamin D and 40% of the folic acid. Considering both dietary and supplementary sources, 44% of the women still had inadequate intake of folic acid (Arkkola, et al., 2006).

iv. Guidelines for Natural Health Products use during pregnancy

Several guidelines have been published by different international organizations (Ingram, 2004; Wilson, 2007) in an effort to improve the nutritional and health

status of pregnant women and to lower the risk of the occurrence of congenital defects in the newborn. Such guidelines focus on NHPs, especially multivitamin and mineral supplements, in addition to optimal dietary intake in the gestational period. For the purposes of this thesis, guidelines issued by the Institute of Medicine in the United States and by Health Canada were reviewed.

- Institute of Medicine

Since 1941, dietary reference intakes (DRIs) have been released by the IOM in which prenatal nutrient requirements from food sources are discussed in detail (IOM, 2002). In order to provide optimal nutritional care to pregnant women, an implementation guide for all primary care practitioners was released by the IOM (IOM, 1992). The use of supplements in addition to the consumption of a nutritionally balanced diet is recommended. However, the IOM also advises on the cautious use of supplements, due to the possibility of nutrient imbalances, excesses or toxicities (IOM, 1992). A prenatal multivitamin/mineral supplement with the following composition should be used by women that posses a higher risk of nutritional deficiencies.

Table 3. Suggested composition of prenatal multivitamin/mineral supplements

Medicinal Ingredient	**Quantity per day**
Iron	30-60 mg
Zinc	15 mg
Copper	2 mg
Calcium	250 mg

Vitamin D	10 μg (400 IU)
Vitamin C	50 mg
Vitamin B6	2 mg
Folate	300 μg
Vitamin B12	2 μg

Adapted from the Institute of Medicine "Nutrition During Pregnancy and Lactation: An Implementation Guide (1992)."

Recommendations for single-nutrient supplements have also been considered in different IOM reports (IOM, 1992; IOM, 1998). In the case of folic acid, the IOM advises the intake of 600 micrograms daily for pregnant women; this dose includes the amount found in food and the synthetic form found in supplements (IOM, 1998). As for vitamin D, recommendations regarding the intake of a single-nutrient supplement have not been specified by the IOM. Calcium content of a multivitamin/mineral supplement should not exceed 250 mg per dose as it may interfere with iron absorption. Calcium supplements, either in a single form or as part of a multivitamin, should be taken with meals to promote effective absorption (IOM, 1992). Iron supplementation is routinely recommended to prevent iron deficiency anemia (IDA) (IOM, 1998); and the IOM recommends the use of iron supplements for all pregnant women beginning at the 12th week of gestation. Iron supplements should include 30 mg of elemental iron per day even if it is part of a multivitamin (IOM, 1992). For women with a higher risk of developing anemia throughout gestation, a higher dose is recommended between 60 to 120 mg of elemental iron per day. As soon as normal haemoglobin levels are achieved, the dose can be lowered to 30 mg/day (IOM, 1992).

- Health Canada

To ensure proper nutrition among the pregnant population, Canada's Food Guide provides the necessary information so that women can meet their nutrient needs (Katamay, 2007). However, the required levels of some nutrients can be difficult to obtain from food sources solely. This was observed in a population survey in 2008 where a large percentage of Canadian women had inadequate intakes for folic acid and iron (Health Canada, 2008). In an effort to increase nutrient intake and prevent any deficiency from developing during gestation, Health Canada released "Prenatal Nutrition Guidelines for Health Professionals" in which pregnant women are advised to include a multivitamin supplement containing 0.4 mg of folic acid as well as 16 to 20 mg of iron. These multivitamins should also contain 400 mcg of vitamin B_{12} (Health Canada, 2009). Women are warned not to take more than one daily dose of their multivitamin to avoid exceeding the upper limit (UL) of some micronutrients (Health Canada, 2009). There are no pregnancy specific recommendations regarding vitamin D and calcium supplementation. Pregnant women are also recommended to look for the DIN or the NPN on the product label indicating that the product has been government approved for its safety, efficacy and quality (Health Canada, 2009). In the same manner, pregnant women are advised to read labels of NHPs as some may include cautionary notes if used during pregnancy and lactation (Health Canada, 2009).

II.6 Role of key micronutrients during gestation

a. Folic Acid

Periconceptional intake of folic acid has been the subject of extensive research in the past decade. Conclusive evidence of its preventive properties against congenital defects is widely available. Folic acid is critical for optimal development of the fetus as it is involved in many essential cellular reactions; it is also required for the expansion of red blood cell mass, the enlargement of the uterus and the growth of the placenta (Scholl, et al., 2000). A higher need for folic acid results from the increased rate of cellular division and tissue growth present from the moment of implantation (Bailey, et al., 2000). Marginal intake of folic acid, even before gestation, can impair cellular growth of the fetus, and other unfavourable outcomes including: low birth weight, spontaneous abortions and NTDs (George, et al., 2002). Therefore, adequate intake of folic acid should begin before pregnancy.

Consequences that may occur when maternal folic acid intake is marginal are associated with the occurrence of different congenital defects. In addition, the impairment of cellular growth can also increase the risk of spontaneous or preterm delivery as well as intrauterine growth restriction (IOM, 1990). As the fetus' spinal cord and brain originates from the neural tube in very early stages of gestation, inadequate folic acid intake before gestation affect the proper development of such (Lindzon and O'Connor, 2007). The two most common defects of the neural tube are spina bifida and anencephaly. Spina bifida is characterized by the absence of vertebral arches through which the spinal membranes and spinal cord may protrude, while anencephaly is characterized by the absence of the brain and cranial vault (Lindzon and O'Connor, 2007).

Since the fortification of the Canadian food supply with folic acid in 1998, studies report a significant reduction in NTDs. In 2003, De Wals and others observed a 32% reduction in affected live births, selective terminations and stillbirths in the province of Quebec and they attributed the decrease to fortification rather than supplement use (De Wals P, et al., 2003). Persad and colleagues observed a decrease of 54% in the incidence of open NTDs in Nova Scotia after a retrospective analysis of clinical records during 1991-1997 and 1998-2000. After the mandatory fortification was implemented the incidence of open NTDs decreased from 2.58 per 1000 births during 1991–1997 to 1.17 per 1000 births during 1998–2000 (RR 0.46, 95% CI 0.32–0.66) suggesting a beneficial effect of fortification policies (Persad, et al., 2002). Finally, a cross-sectional study from Newfoundland reported an improved status of serum folate in 365 pregnant women after fortification. Improved folate status was associated with a decreased incidence of NTDs from 4.67 (1992-1996) to 1.01 (1998-2000) per 1,000 births (House, et al., 2006).

Despite the previous results, it has been estimated that a diet following Canada's Food Guide will provide only 0.2 milligrams (200 micrograms) of folic acid per day. Thus adequate intake of folic acid through diet alone has been questioned for women of childbearing age (Millar, 2004). Supplementation provides an alternative strategy to achieve current recommended intakes for folic acid in the periconception/prenatal period. The Canadian Community Health Survey in 2000/01 showed that 45% of female respondents aged 15 to 55 (estimated 1.5

million women) had used a vitamin supplement containing folic acid routinely before their last pregnancy (Béland, 2002).

The role of folic acid in the prevention of other congenital defects has been debated and remains unclear (Scholl, et al., 2000). Wilcox et al concluded that daily folic acid supplementation of 400 micrograms decreased the risk of isolated cleft lip, but the same results were not observed for cleft palate alone (Wilcox, et al,. 2007). Badovinac and colleagues reported a protective effect of folic acid supplementation against oral clefts (Badovinac et al. 2007).

b. Vitamin D

Vitamin D as 1, 25-dihydroxyvitamin D (1,25-OH_2D) is responsible for adequate calcium and phosphorus absorption in the intestine, bone mineralization and bone metabolism in adults (Kovacs,2008; Narchi, et al., 2010). During pregnancy, vitamin D is required for the optimal calcification of the fetal skeleton due to its involvement in the absorption and utilisation of calcium, especially during the later stages of pregnancy (Williamson, 2006; Hollis, et al., 2006). Food sources of vitamin D are limited and sunlight exposure becomes the main source of this vitamin (Picciano, 2003). The recommended dietary allowance (RDA) for vitamin D is 600 IU/day (IOM, 2010). Plasma levels of 25-cholecalciferol are sensitive to maternal intake and provide a reliable measure of current vitamin D status, as it is proportional to dietary intake and skin exposure to ultraviolet light (Picciano, 2003; Hollis, et al., 2006; Narchi, et al., 2010).

Maternal vitamin D stores are depleted during the last trimester of pregnancy, as a result of fetal development and the incorporation of calcium into the fetal skeleton

(Canadian Paediatric Society, 2007). Women with darker skin pigmentation, inadequate dietary intake and insufficient exposure to ultraviolet light possess a greater risk of developing vitamin D deficiency (Canadian Paediatric Society, 2007). Several studies have documented that some women are vitamin D deficient before and during pregnancy (Nesby-O'Dell et al. 2002a; Dawodu et al. 2003; Sachan et al. 2005a; Schroth et al. 2005b). Circulating levels of 20 ng/ml (50 nmol/L) of 25-OHD have been used to diagnose hypovitaminosis D in adults in several studies (Holick, 2002; Dawson-Hughes, et al., 2005; Hollis, 2005). More recently, smaller size and dental malformations have been observed in babies born from vitamin D deficient mothers (Canadian Paediatric Society, 2007). Javaid and others reported a reduced bone size and bone mineral content of children of nine years of age when mothers had insufficient concentrations of 25-OHD during the last trimester of gestation (Javaid, et al., 2006). In Canada, vitamin D deficiency during pregnancy has raised concerns after 104 cases of rickets were reported between 2002 and 2004. The majority of affected children were First Nations and Inuit who often live in communities where sun exposure is limited during winter months (Ward, et al., 2007). Previous studies have reported a higher prevalence of vitamin D deficiency in Aboriginal women when compared to non-Aboriginal women after adjusting for dietary intakes (Weiler, et al., 2007). Supplementation with vitamin D during the last trimester of pregnancy has produced inconclusive results, as studies suggest that women entering pregnancy with inadequate levels will remain deficient to the end of gestation regardless of supplement use (Hollis, et al 2004). Datta and colleagues concluded that after supplementing pregnant

women with 800-1600 IU of vitamin D for the duration of the pregnancy circulating 25-OHD increased from 5.8 to 11.2 ng/mL; however, this increase remained below 25 ng/mL (Datta, et al., 2002). Vitamin D supplementation during pregnancy remains unclear as it has been suggested that current recommendations may be inadequate for a population with a higher risk of deficiency (Hollis, et al., 2004;Kovacs, 2008).

c. Calcium

Pregnancy increases calcium requirements, especially during the later stages of pregnancy; approximately an additional 300 mg per day during the last quarter (Williamson, 2006). However a more efficient absorption (secondary to a higher concentration of 1, 25-dihydroxyvitamin D3), utilisation (stimulated by estrogen, lactogen and prolactin) and a lower excretion of this mineral (by the re-absorption of calcium in the kidney tubules) prevent the need of an increased dietary intake and provide the fetus with its calcium demands (King, 2000; Kovacs, 2005; Williamson, 2006). As a result, calcium requirements remain the same for pregnant as well as for non pregnant women with a RDA of 1,300 mg /day if pregnancy occurs before 18 years of age and 1000 mg/day for women $\geq$18 years old (IOM, 2010).

Fetal bone growth and mineralization depends primarily on maternal calcium absorption; followed by calcium mobilization from the skeleton (Prentice, 2003; Prentice, 2003a). Physiological changes in absorption may reduce the dietary requirement of calcium (Prentice, 2003a; Olausson, 2008), however, maternal calcium stores may be rapidly depleted if dietary calcium is inadequate, affecting

maternal bone mass and impairing bone development of the fetus (Chang, 2003). Women whose calcium intake is low and who have repeated pregnancy cycles are at a higher risk of developing calcium deficiency (Thomas, 2006; Jarjou, 2010). The extent of the loss of bone density during pregnancy in women with calcium deficiency remains unclear as studies have reported contradictory results (More 2001; Ulrich 2003; Kaur, 2003; Pearson 2004).

Recommendations for calcium supplementation during the gestational period have been controversial, as recent studies suggest re-evaluation of current evidence regarding the beneficial effects of calcium supplementation on maternal and fetal bone health (Prentice 2000; Prentice 2000a; Janakiraman, 2003; Chang, 2003). It has been suggested that calcium requirements during pregnancy have not been fully examined. The need to observe calcium mobilization more closely in order to make recommendations regarding the use of calcium supplements in pregnancy has been discussed in previous publications (Janakiraman, 2003; Thomas, 2006). Supplements that contain amounts to meet the dietary recommendations have been suggested to improve overall calcium intake and prevent the loss of maternal bone mass (Thomas, 2006). The same benefit of calcium supplementation has not been observed in improving fetal growth (Thomas, 2006). Abalos and colleagues studied the effect of calcium supplementation during pregnancy and its effects on fetal growth in utero (Abalos, 2010). Fetal measurements were recorded at 20, 24, 28, 32 and 36 weeks of gestation with an ultrasound at each time point while birth weight and birth length, and head, abdominal and thigh circumferences were recorded at delivery. In this randomised study, calcium supplementation (1500

milligrams per day) had no effect on either somatic or skeletal growth, and no neonatal anthropometric differences were observed between placebo and experimental groups (Abalos, 2010).

Recently, calcium supplementation has also been associated with the prevention of preeclampsia and its complications. High blood pressure during pregnancy is one of the major causes of maternal morbidity and mortality as well as perinatal morbidity and mortality (Moodley, 2008). In a systematic review by Hofmeyr and others, calcium supplementation and its effect on maternal hypertensive disorders was assessed (Hofmeyr, 2003). Only randomised trials using daily calcium supplements containing at least 1000 milligrams were considered. The main findings suggest a modest reduction in the risk of preeclampsia when calcium supplements were used (RR 0.68, 95% CI: 0.57-0.81). A greater benefit was observed in a women with a higher risk of preeclampsia (RR 0.21, 95% CI 0.11-0.39) or in those where calcium intake was low (RR 0.32, 95% CI 0.21-0.49) (Hofmeyr, 2003).

d. Iron

Requirements of iron are higher during pregnancy to assist in the growth of the fetus and the placenta, in addition to being necessary for maternal red blood cell production (Williamson, 2006). Maternal iron stores are the main iron supply of the fetus, which accumulates most of its iron during the last trimester of gestation (Williamson, 2006). Although enhanced intestinal absorption is present (approximately 3 mg/day) the RDA of 27 mg/day (IOM, 2001), is not often met

by this sub-group of the population and it is difficult to achieve through diet alone (Beaton, 2000; Cogswell, et al., 2003).

Iron deficiency during gestation is the main cause of maternal anemia, which has been associated with low birth weight, premature delivery and low iron stores in the neonate (Scholl, et al., 2000). In 2001 the World Health Organization reported that approximately 60% of the pregnant population in developing countries and approximately 18% of pregnant women in industrialized countries suffer from anemia (WHO, 2001). Although most of these women were anemic prior to conception, iron deficiency during the early gestational period can develop into anemia in later stages of pregnancy, despite entering pregnancy with adequate iron stores (Simpson, et al., 2010). Hemoglobin levels lower than 9 g/dl (90g/L), usually a sign of severe anemia, have been associated with an increased risk of maternal and fetal complications (Steer, 2000).

Anemic mothers have an increased risk of delivering low birth weight babies, as studies have found a higher relative risk when maternal hemoglobin levels are lower than 10.4 g/dl (104 g/L) at 13-24 weeks of gestation (Allen, 2000). Levy and colleagues also found a significant association between IDA and low birth weight despite adjusting for gender, ethnicity and gestational age (OR = 1.1; 95% CI = 1.0 -1.2; p = 0.02) when comparing pregnancy and delivery outcomes of women with and without anemia. In addition, placental abruption, placenta previa, labor induction and preterm deliveries were seen in anemic compared with non-anemic women (Levy, et al., 2005). Scanlon and colleagues observed a negative correlation between hemoglobin levels and preterm delivery using data from

173,031 women, where severity of the anemia was associated with preterm delivery (Scanlon, et al., 2000).

As studies consistently report that dietary iron requirements are barely met through diet by the pregnant population worldwide, pharmaceutical supplementation has been suggested as a prudent intervention to prevent IDA and its complications (Beaton, 2000; Cockell, et al., 2009; Simpson, et al., 2010). Maternal iron supplementation has been shown to decrease the incidence of low birth weight infants when compared to mothers who did not supplement during gestation (4% versus 17%); incidence of preterm low birth weight infants (3% versus 10%) was also affected (Cogswel et al., 2003). Additionally, iron stores are less severely depleted by the third trimester when iron supplementation is administered during early stages of gestation (Allen, 2000). Studies from developed countries with non-anemic, iron-sufficient pregnant populations concluded that iron supplementation significantly increased birth weight, in addition to reducing the incidence of low birth weight, and preterm delivery (Siega-Riz, et al., 2006).

II.7 Conclusions

Healthy eating during pregnancy is essential for the mother and the fetus. Nevertheless, in some cases nutrient requirements for key micronutrients are not being met through food intake alone. Even in developed countries, such as Canada, pregnant women have inadequate dietary intake of some vitamins and minerals. Several studies have observed that the majority of the obstetric population have inadequate intakes of vitamins and minerals. This has been

documented by low blood levels of certain nutrients or dietary records showing deficient intakes during pregnancy. Natural Health Products have been recommended, especially vitamin and mineral supplements, during the periconceptional period and the gestational period, with the intention of increasing micronutrient intake and status. Despite this, several studies reported that supplement users in different countries still have inadequate levels of folic acid, vitamin D, calcium and iron when considering food and supplement sources. It is important to note, that even lower levels of such micronutrients were observed, when NHPs were not used. There is growing evidence regarding the beneficial effects of the use of certain NHPs such as vitamin and mineral supplements. Information about supplement intake of pregnant women in Alberta is lacking. The Alberta Pregnancy Outcomes and Nutrition study provided an opportunity to further investigate this issue in a comprehensive manner during each trimester of pregnancy.

CHAPTER III SUBJECTS and METHODS

The Alberta Pregnancy Outcomes and Nutrition (APrON) Study is a cohort study which began in 2008 in Edmonton and Calgary, Alberta. The main objective of APrON is to investigate the relationship between maternal nutrient status during pregnancy and the effects on maternal mental health, as well as the health and development of the children. The current thesis research is based on participants in cohort I (first 600) recruited between June 2009 and June 2010. Details of recruitment, inclusion criteria, data collection and statistical analyses are described below.

III.1 Recruitment

The APrON study was conducted simultaneously in two different locations in the province of Alberta. While most of the recruitment strategies were shared, some differences exist between Edmonton and Calgary due to the manner in which obstetrical care is provided.

In Edmonton, posters of the study were placed in offices of family doctors and midwives in different areas of the city. Also, gynaecologists and obstetricians offices faxed the contact information of patients who had expressed interest in APrON, and who had given permission to be contacted by one of APrON's research assistants to receive more details about the study. Up to August 2010, there were five media releases in local TV and radio stations and the principal investigator of the study in Edmonton, discussed the APrON study. The media

coverage for APrON also included local newspapers and non-profit magazines, and advertisements in maternity magazines. Posters were also put up in maternity stores in different shopping malls; and on-site community recruitment was carried out in malls, recreational centers, and community fairs.

In Calgary, family doctors refer pregnant women to one of "The Primary Care Network" prenatal clinics as soon as pregnancy is confirmed. When women attended their first appointment in the prenatal clinic, nurses or research assistants approached them with information about the APrON study (brochures and contact information of the study personnel). Some radiology offices were also available to APrON staff to contact pregnant women at the time of their first or second ultrasound between the twelfth and eighteenth week respectively. Posters of the study were placed in doctors and midwives' offices and extensive media coverage also occurred in Calgary.

APrON has an official webpage (www.apronstudy.ca) where prospective participants can obtain more detailed background about the study, become familiar with the principal investigators, science advisors, graduate students and other staff involved with the study. An online form requesting to be contacted by one of the research assistants is also available.

III.2 Subjects

Inclusion criteria to participate in APrON included: (1) women residing in Calgary, Edmonton or surrounding areas, (2) $\leq$ 27 weeks of gestation, (3) 16

years of age or older (if participants were under 18 years of age, parental consent was required), and (4) able to speak and write English and provide a written consent form for herself and her child to participate in APrON. Participants' information was obtained from a structured questionnaire that pregnant women completed during their first visit to APrON. The questionnaire included questions about demographic characteristics, lifestyle variables, past medical history and health status. Based on the necessary power calculations for the analysis of different APrON sub-studies and in order to standardize sample sizes between them, a total of 600 women were considered for the initial cohort analyses, including the present study.

III.3 Supplement Intake Questionnaire (SIQ)

The SIQ was specifically developed for the APrON study based on questionnaires used in previous studies where dietary supplement intake was assessed (Statistics Canada 2004; CDC 2006; Csizmadi, et al., 2006). Moreover, the SIQ was adapted to evaluate the use of NHPs by pregnant women specifically. Prior to its official use with APrON participants, the SIQ was pilot tested with a panel of nutrition experts. Subsequent testing, involving the use of the SIQ with the first 50 participants in the study during their first and second visits was done in order to determine if data were being collected in an efficient manner and if enough detail regarding micronutrient content was reflected with the SIQ. Modifications were made as necessary; and minor wording and formatting changes were made. Columns were added to simplify its use during follow-up visits rather than using a new SIQ each time. This adjustment enhanced data collection as participants were

able to report changes in products, frequency, or dose based on their previous report.

The final version of the SIQ consisted of three sections that requested information about intake of NHPs. The first section listed options for multivitamins/minerals, the second section listed single nutrient supplements and the third section consisted of herbal products, probiotics, homeopathic remedies, or other products such as amino acids, essential fatty acids or traditional medicines. Commonly used formulations were included as a checklist. For situations where a product was not listed, but it was consumed by a participant, space was available to record the name and manufacturer of the NHP as well as the NPN or DIN if available.

At each visit, participants were asked to bring the containers or labels for all of the NHPs that they were consuming. The frequency of intake and dosage was recorded for each NHP. If participants were unable to provide the container(s) of the NHPs, a follow-up phone call was made to obtain the information needed and a reminder e-mail was sent to participants for the subsequent visits.

The APrON participants reported to the research unit on one occasion in each trimester of gestation (ideally participants were recruited during the first trimester of pregnancy) and once at three months post-partum. Data for this study include only the gestational visits. During their appointments participants completed a dietary interview consisting of a 24-hour recall followed by the SIQ.

III.4 Supplement Intake Database

One of the objectives of this study was to develop a database of all of the NHPs that APrON participants were taking during pregnancy, with the intention of providing a more accurate description of their micronutrient intake. To facilitate the entry of the micronutrient content of different formulations, either a NPN or a DIN was used. Health Canada, under the Natural Health Products Directorate (NHPD), assigns an eight digit numerical code to each NHP that has complied with official regulations, to indicate that it has been assessed for its quality, safety and efficacy (Health Canada, 2003). The same code was used to identify NHPs in the APrON database. Micronutrient content was entered according to Health Canada's Natural Health Product Database for products with a valid NPN/DIN. Whenever a NPN/DIN was non-existent, nutrient information was recorded either from the label or the container of the product(s). In cases where NHPs were purchased from the internet or another country, nutritional information was obtained from the website of the manufacturer or the supplier. In either cases, NHPs were specifically coded for the purposes of this study.

When all methods were used and nutrient information was still unavailable, the most common formulations of NHPs were used as a default. For example, for prenatal multivitamin/mineral products, Centrum Materna by Wyeth Consumer Healthcare Inc. with NPN 80001842 was used, as it was the most popular product among APrON participants. The default values for folic acid (1000 mcg), vitamin

D (400 IU), calcium (250 mg) and iron (35 mg) were based on the values of these nutrients for the most commonly reported NHPs taken by participants.

For nutrient calculation from all of the NHPs in the study, an Excel database (Microsoft Office 2007) containing the nutrient value of more than 400 NHPs was developed and subsequently updated on approximately a bi-weekly basis. A second database was simultaneously developed in which every NHP code was recorded for each gestational time point for each participant. After data collection of the 600 participants was finalized, both databases were merged into an Access database (Microsoft Office 2007) to obtain the total intake of folic acid, vitamin D, calcium and iron for each trimester from all the NHPs that participants reported taking during their pregnancy visits. With the SIQ and the micronutrient database developed, not only the key micronutrients of this thesis were recorded but also other nutrients involved in pregnancy such as choline, iodine, zinc, DHA, AHA, among others. Furthermore, the database developed provided a more detailed record on micronutrient intake providing a reliable tool for measuring NHPs intake throughout gestation.

To evaluate intake of folic acid, vitamin D, calcium and iron from NHPs among participants, the IOM and Health Canada's recommendations for pregnancy were used.

III.5 Statistical Analysis

Statistical analyses were done using SPSS for Windows version 17.0. ANOVA was used to assess differences between trimesters for continuous variables using

Bonferroni post-hoc test on statistically significant results. The chi-square statistic was used to test differences involving categorical variables. All statistical tests were two-sided and performed at the $p<0.05$ level of significance.

III.6 Ethics

Approval for this study was provided by the Health Research Ethics Board, University of Alberta and the Health Research Ethics Board, Faculty of Medicine, University of Calgary.

CHAPTER IV RESULTS

IV.1 Participant characteristics

Six hundred pregnant women were enrolled in the APrON Study between June 2009 and June 2010 between Edmonton and Calgary; however, different sample sizes were observed in each trimester due to drop-outs between trimesters or missed appointments. One participant was completely excluded because of lack of data in all three visits leaving a total of 599 participants in this study. At enrolment, the mean age of the participants was 31 (±4.3) yr and the mean pre-pregnancy body mass index (BMI) was 24.1 (±4.9). The majority of the women were Caucasian (81%) and were married or in a stable relationship (90%). Approximately 45% of the subjects had a university degree and about 50% reported an annual family income above $100,000. Fifty four percent of the participants reported having at least one previous pregnancy and the majority had planned their current pregnancy (76%) with 6% of them having an assisted pregnancy. Table 4 provides a more detailed description of the demographic characteristics of the APrON Study participants.

Table 4.
Characteristics of participants enrolled in the APrON Study

Demographic variables at first visit (n = 599)	
Age, ($\bar{x}$ ± SD)[1]	31.1 (± 4.3)
Pre-pregnancy BMI[2], ($\bar{x}$ ± SD)	24.1(± 4.9)
Marital Status, (%)[3]	
• Single / separated / divorced	3.3
• Married or in a stable relationship	90.5
Highest level of education, (%)	
• Less than high school	1.7
• High school	7.7
• Trade	19.3
• University	44.8
• Post Graduate	19.8
Ethnicity, (%)	
• Caucasian	81.0
• Chinese	2.5
• Latin American	2.3
• Black	1.2
• Other	6.2
Total Family Annual Income, (%)	
• Less than 20K	1.5
• 20-39K	4.0
• 40-69K	12.5
• 70-99K	23.3
• 100+	50.8
Previous Pregnancies, (%)	
• Yes	54.2
• No	40.0
Current Pregnancy Planned, (%)	
• Yes	76.5
• No	17.7
Assisted Pregnancy, (%)	
• Yes	6.5
• No	87.5

[1] $\bar{x}$, mean; SD, standard deviation.
[2] Calculated by (kg / m^2)
[3] Column percentages may not add up to 100% due to missing data

IV.2 Use of Natural Health Products by pregnant women during each trimester

Use of NHPs reported by APrON subjects is illustrated in Table 5. Significant differences were observed in the reported intake of multivitamin supplements between trimesters whereby 97% of participants reported their use in the first trimester, which decreased to 92% by the third trimester (p=.009). A significant difference was also noted in the reported intake of single-nutrient supplements. Forty-five percent of pregnant women indicated their use in the first trimester, with a ten percent increase by the third trimester (p=0.01). There were no significant differences in the reported intake of other NHPs such as herbal products, amino acids and essential fatty acids, homeopathic remedies, traditional medicine and probiotics between trimesters (Table 5). In a sub-sample of pregnant women who attended all three pregnancy visits (n=105), one per trimester, no significant differences were observed in the intake of NHPs between trimesters. Table 6 describes the reported intake of NHPs among those participants who attended the APrON study in all three trimesters. Due to the low proportion of participants reporting the use of herbal products, a list of the most common formulations is observed in Appendix E.

Table 5.
Natural Health Products consumed on a daily basis by participants in APrON[1].

First Trimester (n = 136)		Second Trimester (n = 575)		Third Trimester (n =516)		
Natural Health Products	n (%)[2]	**Natural Health Products**	n (%)	**Natural Health Products**	n (%)	P [3]
Multivitamin/mineral	132 (97)[a]	Multivitamin/mineral	551 (95)[a]	Multivitamin/mineral	475 (92)[b]	.009[4]
Single nutrient	62 (45)[a]	Single nutrient	270 (46)[a]	Single nutrient	284 (55)[b]	.015[5]
Herbal products	13 (9)	Herbal products	52 (9)	Herbal products	31 (6)	.128
Amino acids / EFAs[6]	34 (25)	Amino acids / EFAs	129 (22)	Amino acids / EFAs	144 (27)	.114
Homeopathic Remedies	2 (1)	Homeopathic Remedies	9 (1)	Homeopathic Remedies	4 (0.7)	.476
Traditional Medicine[7]	0	Traditional Medicine	0	Traditional Medicine	0	NS[8]
Probiotics	6 (4)	Probiotics	18 (3)	Probiotics	20 (3)	.691

[1] As reported by participant as daily intake at each visit.
[2] Column percentages do not add to 100 as participants reported the use of ≥1 different NHPs.
[3] P value from the Chi square statistic for categorical variables with significance at the $p<0.05$ level.
[4] Significant difference of multivitamin intake between trimesters shown by [a], [b].
[5] Significant difference of single supplement intake between trimesters shown by [a], [b].
[6] EFAs, essential fatty acids
[7] Traditional medicine refers to indigenous skills and practices of different cultures, used in the maintenance of health, prevention, diagnosis, improvement or treatment of physical and mental illness.
[8] NS, not significant

Table 6.

Natural Health Products consumed on a daily basis by a subgroup of participants who attended all three pregnancy visits in APrON (n=105)[1].

First Trimester		Second Trimester		Third Trimester		
Natural Health Product	***n* (%)[2]**	**Natural Health Product**	***n* (%)**	**Natural Health Product**	***n* (%)**	***P*[3]**
Multivitamin/mineral	103 (98)	Multivitamin/mineral	99 (94)	Multivitamin/mineral	96 (91)	.100
Single nutrient	47 (44)	Single nutrient	53 (50)	Single nutrient	63 (60)	.083
Herbal products	10 (9)	Herbal products	6 (5)	Herbal products	4 (3)	.224
Amino acids/EFAs[4]	26 (24)	Amino acids/EFAs	23 (21)	Amino acids/EFAs	28 (26)	.721
Homeopathic remedies	1 (1)	Homeopathic remedies	2 (1)	Homeopathic remedies	1 (1)	.776
Traditional medicine[5]	0	Traditional medicine	0	Traditional medicine	0	NS[6]
Probiotics	4 (3)	Probiotics	1 (1)	Probiotics	2 (1)	.360

[1] As reported by participant as daily intake in each visit.
[2] Column percentages do not add to 100 as participants reported the use of ≥1 different NHPs.
[3] P value from Chi square statistic for categorical variables with significance at the $p<0.05$ level.
[4] EFAs, essential fatty acids.
[5] Traditional medicine refers to indigenous skills and practices of different cultures, used in the maintenance of health, prevention, diagnosis, improvement or treatment of physical and mental illness.
[6] NS, not significant

IV.3 Contribution of Natural Health Products in meeting *dietary* recommendations

Micronutrient intake of APrON participants from NHPs was compared with the RDA for pregnancy from IOM recommendations. Daily reported intake of folic acid, vitamin D, calcium and iron from NHPs was analyzed in each trimester (Table 7). Dietary intake was not included in this analysis. Average folic acid intake from NHPs as reported by participants was greater than 200% of the daily recommendation for the gestational period in each trimester, with mean intakes above 1200 micrograms per day. No significant differences were observed between trimesters. The mean reported intake of vitamin D from NHPs (~700 IU) was enough to meet 100% of the current RDA (600 IU) with no significant differences observed between trimesters. Non-dietary calcium intake during pregnancy was responsible for meeting approximately 25-30% of dietary recommendations (1000 mg). Mean calcium intake was approximately 300 milligrams in each trimester and no significant differences were observed between trimesters. Significant differences were observed in iron intake between trimesters. While approximately 104% (28.2 ± 16.6 milligrams) of the RDA was met by the use of NHPs during the first trimester, an increase to 144% (38.7 ± 33.4 milligrams) was reported by the third trimester (p=0.000). In a sub-sample of participants who attended all three pregnancy visits (n=105) no significant differences were observed in the mean intake of folic acid, vitamin D, calcium or iron between trimesters. However, reported intakes of micronutrients from NHPs were above the RDA for folic acid, vitamin D and iron (Table 8).

Table 7.
Daily intake of key micronutrients from Natural Health Products during pregnancy.

	First Trimester (n = 136)		Second Trimester (n = 575)		Third Trimester (n =516)		
Micronutrient	**$\bar{x}$ ± SD[1]**	**Median (min, max)[2]**	**$\bar{x}$ ± SD**	**Median (min, max)**	**$\bar{x}$ ± SD**	**Median (min, max)**	***P*[3]**
Folic Acid (mcg)	1225.3 ± 865.8	1000 (0, 6000 mcg)	1352.6 ± 1109.7	1000 (0, 7100 mcg)	1228.2 ± 1029.3	1000 (0, 6023 mcg)	.126
(% RDA)[4]	204 ± 144		225 ± 184		204 ± 171		
Vitamin D (IU)	788.7 ± 1302.0	400 (0, 12600 IU)	643.6 ± 670.0	400 (0, 6000 IU)	746.3 ± 1001.7	400 (0, 9500 IU)	.084
(% RDA)	131 ± 217		107 ± 111		124 ± 166		
Calcium (mg)	312.5 ± 313.1	250 (0, 2300 mg)	338.9 ± 296.6	250 (0, 2300 mg)	351.7 ± 338.7	250 (0, 2300 mg)	.421
(% RDA)	31 ± 31		33 ± 29		35 ± 33		
Iron (mg)	28.2 ± 16.6[a]	27 (0, 160 mg)	30.3 ± 20.6[a]	27 (0,187 mg)	38.7 ± 33.4[b]	27 (0, 227 mg)	< .001[5]
(% RDA)	104 ± 61		112 ± 76		143 ± 124		

[1] $\bar{x}$, mean; SD, standard deviation.
[2] Min, minimum; max, maximum
[3] *P* value for ANOVA for continuous variables with significance at the p<0.05 level.
[4] RDA, Recommended Dietary Allowance; folic acid = 600 mcg/day, vitamin D = 600 IU/day, calcium = 1000 mg/day, iron = 27 mg/day
[5] Significant differences for iron between groups with Bonferroni post-hoc test shown by [a], [b].

Table 8.
Daily intake of key micronutrients from Natural Health Products during pregnancy in a subgroup of participants who attended all three pregnancy visits (n=105).

	First Trimester		Second Trimester		Third Trimester		
Micronutrient	**$\bar{x}$ ± SD[1]**	**Median (min, max)[2]**	**$\bar{x}$ ± SD**	**Median (min, max)**	**$\bar{x}$ ± SD**	**Median (min, max)**	***P*[3]**
Folic Acid (mcg)	1223.3 ± 961.2	1000 (0,6000)	1240.0 ± 1003.2	1000 (0,6100)	1155.5 ± 892.8	1000 (0,6000)	.878
Vitamin D (IU)	857.2 ± 1450.5	400 (0,12600)	708.4 ± 766.6	400 (0,3775)	998.6 ± 1421.8	400 (0,9500)	.397
Calcium (mg)	327.7 ± 346.2	250 (0,2300)	336.2 ± 335.5	250 (0,2300)	345.8 ± 348.8	250 (0,2300)	.240
Iron (mg)	28.7 ± 18.4	27.0 (0,160)	30.8 ± 23.4	27.0 (0,187)	36.8 ± 30.8	27 (0,160)	.171

[1] $\bar{x}$, mean; SD, standard deviation.
[2] Min, minimum; max, maximum
[3] *P* value for repeated measures ANOVA for continuous variables with significance at the $p<0.05$ level.

IV.4 Compliance with *supplementation* guidelines

For the purpose of this thesis, supplementation guidelines from the IOM and Health Canada were considered (Table 9). Reported intakes from supplements of key micronutrients were analyzed in order to determine the proportion of participants who met the established guidelines of the entities mentioned above during each trimester of their pregnancies. The IOM guideline for folic acid supplementation was met by 97% of participants during the first trimester of gestation while decreasing significantly by the third trimester to 91% ($p= 0.02$). Compliance with iron supplementation guidelines was also significantly different between trimesters; while 15% of participants met the guideline in the first trimester, an increase to 29% of participants meeting the guideline was observed during the third trimester ($p = < 0.001$). No other significant differences between trimesters were observed in the proportion of participants meeting the IOM supplementation guidelines for the remaining micronutrients. The proportion of participants meeting the supplementation guidelines during the gestational period for the remaining micronutrients was: vitamin D (~70%) and calcium (~80%). Compliance with supplementation guidelines for all four micronutrients was ~5% in the first trimester, ~9% during the second, and ~11% in the third trimester with no significant differences between trimesters (Table 10).

Demographic characteristics of participants meeting supplementation guidelines for the four micronutrients in at least one trimester ($n= 103$) are described in Table 11. Significant differences were observed in participants with a higher level

education compared to those with lower level of education (p=0.049). Significant differences were also observed regarding the ethnic background between the group of participants meeting the IOM supplementation guidelines for the four micronutrients in at least one trimester compared to the group who did not (p= 0.048).

Health Canada has established guidelines for folic acid and iron supplementation. Significant differences were observed in the proportion of participants meeting Health Canada's folic acid supplementation guidelines from the first trimester, where ~97% of the participants were compliant while ~91% of them were meeting them during the third trimester (p= 0.03). No significant differences were observed in the proportion of participants meeting iron supplementation guidelines between trimesters. The proportion of participants meeting guidelines for both, folic acid and iron was not significantly different between trimesters (Table 12).

Table 9.

Daily supplementation guidelines for pregnancy by the Institute of Medicine[1] and Health Canada[2].

Micronutrient	Institute of Medicine (IOM)[3]	Health Canada[4]
Folic Acid (mcg)	300	400
Vitamin D (IU)	400	NA[5]
Calcium (mg)	250	NA
Iron (mg)	30 – 60	16 – 20

[1] Institute of Medicine. "Nutrition During Pregnancy and Lactation: An Implementation Guide" (1992).

[2] Health Canada. "Prenatal Nutrition Guidelines for Health Professionals" (2009).

[3] For the purpose of this thesis, participants with an intake of 300 mcg *or above* of folic acid, 400 IU *or above* of vitamin D, 250 mg of calcium or above and 30 mg of iron *or above* were considered as meeting guidelines.

[4] For the purpose of this thesis, participants with an intake of 400 mcg *or above* of folic acid, and 16 mg of iron *or above* were considered as meeting guidelines.

[5]NA, not applicable.

Table 10.

Proportion (%) of participants in APrON meeting the Institute of Medicine supplementation guidelines during pregnancy[1].

Micronutrient	First Trimester (n=136)	Second Trimester (n=575)	Third Trimester (n=516)	*P*[2]
	% of participants meeting guidelines for:			
Folic Acid	97[a]	95[a]	91[b]	021[3]
Vitamin D	74	71	68	275
Calcium	79	83	81	559
Iron	15[a]	20[a]	29[b]	<0 001[4]
All four micronutrients[5]	5	9	11	076

[1] For the purpose of this thesis, participants with an intake of 300 mcg *or above* of folic acid, 400 IU *or above* of vitamin D, 250 mg of calcium or above and 30 mg of iron *or above* were considered as meeting guidelines

[2] *P* value from Chi-square statistic for categorical variables with significance at the p<0 05 level

[3] Significant differences for folic acid between groups shown by [a, b]

[4] Significant differences for iron between groups shown by [a,b]

[5] Proportion of participants meeting supplementation guidelines for folic acid, vitamin D, calcium and iron in each trimester

Table 11.

Demographic characteristics of women meeting the Institute of Medicine supplementation guidelines in at least one trimester of pregnancy compared to those who did not meet the guidelines[1].

	Participants meeting guidelines (n=103)[2]	Participants not meeting guidelines (n= 497)	*P*[3]
Age, ($\bar{x}$ ± SD)[4]	30.8 (± 3.2)	31.8 (±4.3)	0.178
Pre-pregnancy BMI, (%)[5]			
Underweight	1.9	3.0	
Adequate	64.1	61.4	
Overweight	19.4	17.1	0.647
Obese	9.7	13.5	
Marital Status, (%)			
Married/common law	89.3	90.7	
Single/separated/divorced	2.9	3.2	0.895
Highest level of education			
Trade or below	20.4	30.2	
University or above	71.8	63.2	0.049
Ethnicity, (%)			
Caucasian	73.8	82.5	
Others	17.5	10.9	0.048
Total Annual Income, (%)			
Low Income[6]	2.9	5.8	
High Income	88.3	86.3	0.235
Previous Pregnancies, (%)			
Yes	49.5	54.9	
No	42.7	39.2	0.403
Current Pregnancy Planned, (%)			
Yes	78.6	76.1	
No	14.6	18.1	0.408
Assisted Pregnancy, (%)			
Yes	9.7	5.8	
No	83.5	88.3	0.138

[1] For the purpose of this thesis, participants with an intake of 300 mcg *or above* of folic acid, 400 IU *or above* of vitamin D, 250 mg of calcium or above and 30 mg of iron *or above* were considered as meeting guidelines.
[2]Participants meeting supplement guidelines for all: folic acid, vitamin D, calcium and iron ≥1 trimester.
[3] *P* value from Chi-square statistic for categorical variables with significance at the $p<0.05$ level.
[4] $\bar{x}$, mean; SD, standard deviation.
[5] Percentages do not add to 100% due to missing data.
[6] Low income cut-off point at $40,000 per year for a family size of 4 individuals in a community with more than 500,000 habitants (Statistics Canada, 2009).

Table 12.
Proportion (%) of participants meeting Health Canada's supplementation guidelines[1].

Micronutrient	First Trimester (n=136)	Second Trimester (n=575)	Third Trimester (n=516)	*P*[2]
	% of participants meeting guidelines for:			
Folic Acid	97[a]	94[a]	91[b]	031[3]
Iron	91	88	88	636
Both micronutrients[3]	91	88	87	415

[1] For the purpose of this thesis, participants with an intake of 400 mcg *or above* of folic acid, and 16 mg of iron *or above* were considered as meeting guidelines
[2] *P* value from Chi-square statistic for categorical variables with significance at the p<0 05 level
[3] Significant differences for folic acid between groups shown by [a], [b]
[4] Proportion of participants meeting supplementation guidelines for folic acid and iron in each trimester

IV.5 Safety concerns regarding the use of Natural Health Products during gestation

Mean intake of folic acid, vitamin D, calcium and iron from NHPs were compared to the Upper Limit (UL) established by the IOM in each trimester of pregnancy (Table 13). Folic acid intake was above the UL for approximately 20% of pregnant women in each trimester with no significant differences between trimesters. Significant differences were observed in the proportion of participants exceeding the UL of vitamin D between trimesters where fewer women exceeded the UL during the second trimester (0.2%) when compared with the first and third trimester (1%) ($p= 0.02$). None of the participants in the study exceeded the UL for calcium in any trimester and finally, the proportion of women who exceeded the UL for iron intake significantly increased from the first trimester (4%) to the third trimester where almost 20% of participants reported intakes above the UL (45 milligrams) ($p=.000$).

Table 13.

Proportion (%) of participants exceeding the upper limit of key micronutrients by the use of Natural Health Products during pregnancy[1].

Micronutrient (UL)[2]	First Trimester (n=136)	Second Trimester (n=575)	Third Trimester (n=516)	*P*[3]
	% of participants			
Folic Acid (1000 mcg)	22	26	21	.234
Vitamin D (4000 IU)	1[a]	0.2[b]	1[a]	.026[4]
Calcium (3000 mg)	0.0	0.0	0.0	NS[5]
Iron (45 mg)	4[a]	9[a]	19[b]	<.001[6]

[1] Dietary intake was not considered.
[2] UL, upper limit (IOM, 2002).
[3] *P* value from Chi-square statistic for categorical variables with significance at the $p<0.05$ level.
[4] Significant differences for vitamin D between trimesters shown by [a], [b].
[5] NS, not significant.
[6] Significant differences for iron between trimesters shown by [a], [b].

CHAPTER V DISCUSSION

Pregnant women in Canada are advised to supplement their diets with NHPs in order to prevent micronutrient deficiencies during gestation and to minimize detrimental conditions that deficiencies may cause for the mother and the fetus. Some NHPs, especially multivitamins and single-nutrient supplements, are recommended to be consumed by pregnant women to support their diet. The present study showed that the use of NHPs was high and remained high in each trimester of pregnancy. However, it is noteworthy that some nutrients were received cumulatively and in large amounts from many different formulations. It is important to consider that mean intakes reported in this study did not reflect dietary intake of the micronutrients reviewed in this thesis: folic acid, vitamin D, calcium and iron. For a more complete assessment of total intake of such micronutrients dietary sources should be included.

Results of this study are consistent with recent pregnancy studies where the majority of the women reported the intake of some type of NHPs (Maats, 2002; Glover, 2003; Refuerzo, 2005; Bercaw, 2010). Furthermore, APrON participants had similar demographic characteristics of supplement users to other studies in different countries (Braekke, 2003; Arkkola, 2006; Foster, 2009); including women who were older, highly educated, with a normal pre-pregnancy BMI and in a stable relationship. In addition, results are consistent with a previous survey carried out by Health Canada, which showed that highly educated women between 18 and 34 years of age, with a high annual income and residing in Alberta were more likely to use NHPs (NHPD, 2005).

The prevalence of multivitamin and single-nutrient supplement use was high in each trimester of pregnancy, with the majority of the women reporting using them. Results showed that more than 90 % of the women used a multivitamin supplement, while almost half of them reported the use of single-nutrient supplements through the course of their pregnancies. An opposite trend was observed between multivitamin and single-nutrient supplements as the pregnancies progressed. While multivitamin use decreased in each trimester, the use of single-nutrient supplements was significantly higher by the end of pregnancy compared to the first trimester. The remaining NHPs were not as commonly used by our sample; however, studies have shown a higher use of essential fatty acids (Haugen, 2007) and herbal products (Tsui, 2001; Glover, 2003) by the obstetric population than that reported in this thesis. Use of both types of NHPs, EFAs and herbal products, remained below 25% and 10% respectively. Results from a sub-group of participants that attended all three pregnancy visits followed the same trend as the main sample but there were no significant differences in the use of NHPs between trimesters.

Dietary recommendations and *supplementation* guidelines for the gestational period have been published by the IOM as well as Health Canada (reviewed in previous chapters) advising women considering becoming pregnant to take a daily multivitamin containing 400 micrograms (Health Canada) or 300 micrograms (IOM) of folic acid supplements throughout gestation. As reported previously, not only were women following such recommendations but their reported intakes indicated that the majority were consuming enough folic acid to meet and in some

cases exceed their daily RDA with NHPs only. Moreover, approximately 20% of participants exceeded the upper limit (UL) (1000 mcg) for folic acid in each trimester of gestation. High doses of folic acid (5000 mcg) are currently advised and prescribed whenever there is a family history of NTDs or if there was a previous pregnancy affected by one (Wilson, 2003). Whether participants using high doses of folic acid were prescribed the amounts higher than 1000 mcg per day is unknown.

The same tendency to meet dietary recommendations with the sole use of NHPs was observed for vitamin D and iron. Participants in the study met more than a 100% of the RDA of these nutrients in each trimester from supplemental sources. It is important to mention that Health Canada does not make recommendations for vitamin D or calcium supplementation during pregnancy and that the IOM only suggests the amount of those micronutrients that should be present in prenatal formulations, which is 400 IU and 250 milligrams respectively. There are few dietary sources for vitamin D, and sunlight exposure becomes the main source of endogenous synthesis of vitamin D. This can be limited in some areas in northern Canada, such as Edmonton, therefore use of NHPs by APrON participants as the main source of vitamin D may not be of great concern. Furthermore, the proportion of participants who had a reported intake beyond the upper limit (4000 IU) of vitamin D was ~1% in the first and third trimester and less than 0.5% during the second trimester. Mean calcium supplement intakes remained constant throughout gestation, representing approximately 30% of the RDA. This amount is also very similar with the suggested content of a prenatal multivitamin according to the IOM,

and there were no participants exceeding the UL for calcium in any trimester. Thus, calcium intake from NHPs appears to be at a reasonable level to supplement dietary intake based on the amount suggested by the IOM supplementation guidelines. Calcium from NHPs should not exceed a concentration of 250 mg in order to prevent an impairment of intestinal absorption of iron (IOM, 1992).

Reported mean intake of iron from NHPs was also observed to be high enough to meet the RDA established for pregnant women (27 mg) in every trimester, increasing significantly as pregnancy progressed; reaching almost 150% of the RDA by the third trimester with NHPs only. Of note, almost 20% of participants reported consuming more than 45 milligrams of iron during the third trimester surpassing the UL. Compliance with iron supplementation recommendations was low in previous studies as a result of its secondary effects such as nausea, vomiting and other gastrointestinal symptoms (Hyder, 2002; Melamed, 2007; Nguyen, 2008); thus, our findings were unexpected as they differ from previous studies. Higher intakes of iron are recommended for women who develop IDA during pregnancy, and this could explain the observed increase; particularly in the third trimester, when blood volume doubles, hemoglobin levels decrease and the risk of developing IDA is higher. In these cases, iron supplementation is prescribed at levels of 60 milligrams per day until hemoglobin reaches normal levels; then iron supplementation can be reduced to 30 mg/day. The same behaviour was observed in participants who had all three pregnancy visits. Micronutrient intake was high enough to meet the dietary recommendations for folic acid, vitamin D and iron with NHPs alone while calcium remained at approximately 30% of the RDA.

Contrary to the main sample, the intake remained constant throughout gestation with no significant differences between trimesters. It is important to mention that in the main sample as well as in the sub-sample of participants attending the three pregnancy visits, a wide range in the intake of the four key micronutrients from NHPs was observed. In each trimester, there were participants with null intake of these micronutrients as well as some reporting very high amounts of them as it can be seen in the minimum and maximum values of Table 7 and Table 8. Secondary to such excessive intakes, the reported means of folic acid, vitamin D, iron and calcium may have been affected resulting in higher mean intakes of these micronutrients.

The IOM suggests micronutrient supplementation of folic acid, vitamin D, calcium and iron at levels to prevent deficiency, but also to avoid excess intake. Compliance with such micronutrient supplementation recommendations was analyzed by single nutrient and per trimester. It was observed that folic acid supplementation recommendations were met by almost all of the participants in the study during the first trimester and a small but significant decrease was observed by the end of their pregnancy. Despite such decline, compliance was reported by more than 90% of the women. Vitamin D and calcium supplementation guidelines were met by fewer participants; however, compliance was observed in approximately 70% of women in the study in the three trimesters. In this study compliance with recommendations to take a supplement was high for those micronutrients, differing from other studies where the proportion of participants meeting the guidelines was low (Millar, 2004). Iron was the only nutrient which

recommended supplementary intake remained below 20% in the first and second trimester, significantly increasing by the third trimester to 30%. As mentioned above, iron supplements have been constantly reported to have low compliance due to its gastrointestinal side effects which can worsen during pregnancy. This trend was observed in this thesis. Since the IOM has outlined specific amounts of supplementation with those micronutrients, compliance with all four nutrients in each trimester was analyzed. Surprisingly, despite having high compliance of single nutrient supplementation, compliance of all four nutrients was low in each trimester with a tendency to meet IOM supplementation guidelines for all four micronutrients during the third trimester. A total of 103 women met the supplementation guidelines for all the key micronutrients in at least 1 trimester of pregnancy. Significant differences in meeting supplementation guidelines were observed in the level of education and ethnic background between the compliant group and the non-compliant. Others have shown (Haugen, et al., 2008) that women with a high level of education (university or above) would be more likely to follow guidelines when compared with participants with lower academic achievement (trade or below). Also, predictions regarding the significant differences observed in ethnic background, Caucasian and non-Caucasian participants, could be made. Ethnic minorities have been reported to be less likely to be compliant with recommendations or have nutrient adequate diets (Jasti, et al., 2003). Therefore, it would be expected that Caucasians would be more likely to meet supplementation guidelines than non-Caucasians. Ethnic minorities in the present study sample were represented primarily by Asian, Latin American, Black

and in a smaller proportion Native Canadians, and they had higher proportional representation in the group complying with the guidelines, than the group that did not.

V.1 Strengths and Limitations

The use of NHPs is becoming a common practice for the general population, and in order to determine nutritional status it has become necessary to consider dietary and supplement sources. However, there has not been an appropriate tool that could reflect micronutrient intake from NHPs, nor one that was targeted specifically for pregnant women. One of the objectives of this study and one of its strengths was the development of a questionnaire (SIQ). The SIQ was used efficiently to record all the different types of NHPs that pregnant women used throughout their pregnancy. Moreover, the SIQ provided the micronutrient content and the frequency of use of NHPs in each trimester of gestation. With the SIQ, it was possible to describe the behaviour of pregnant women regarding NHPs. In addition, the extent to which NHPs were used to meet dietary recommendations was reported as well as the changes in micronutrient intakes as pregnancy progressed; both which have been rarely reported. To complement the SIQ, an extensive database with more than 400 different NHPs, and all the micronutrient content information, was developed. Research on this topic area is limited and yet the information is essential in understanding the nutritional status of the pregnant population. Therefore, the results of this study make an important addition to the literature. One limitation of the study was that the demographic characteristics of the participants may have influenced the overall results. Women with low socioeconomic status,

low academic achievement or women from ethnic minorities may have different behavioural patterns in using NHPs and subsequently may be more at risk of sub-optimal micronutrient intakes. Nutrient intakes may not always reflect nutrient status as there are several factors that may interfere with the process. In some cases, intestinal absorption may be impaired due to nutrient-nutrient interactions, as it occurs between calcium and iron. Also, drug-nutrient interaction may also lead to inadequate absorption. In cases such as vitamin D, nutrient status may not directly reflect dietary intake, as endogenous reactions may increase its plasma levels if adequate environmental conditions are present. Similar to vitamin D, calcium status may not be the direct result of dietary intake as it is highly dependent on physiological adaptations leading to the re-absorption of the mineral by the kidney tubules, and re-absorption is higher during gestation. More recent studies have discussed the role of genetics on nutrient metabolism and requirements as well as the role that nutrients plays in genetic expression. Folic acid is one micronutrient of interest due to its role in DNA methylation reactions. Finally, due to the high mean intakes of folic acid, vitamin D, calcium and iron from NHPs, assumptions about adequate nutrition status may not be applicable.

V.2 Conclusions and Application

Literature describing the use of NHPs in pregnant populations is limited, in part due to the complexity of data collection and reliability of reported intake. The present study aimed to provide a better understanding of supplementation practices by pregnant women in each trimester of gestation. Results demonstrated that the use of NHPs among pregnant women is very common in the APrON cohort.

However, it is important to consider that the population included here represent a small sector of the obstetric population and it is likely that the socioeconomic characteristics of the participants in the study influenced the observed supplement intake habits. As such, the use of NHPs and mean intakes of folic acid, vitamin D, calcium and iron may differ from women who belong to lower socioeconomic status, have lower levels of education, and are members of ethnic minorities or aboriginal groups. As a result, assumptions of an adequate nutrition status or that current supplementation guidelines are being followed are not widely generalizable. The additional nutrients that NHPs provide to the total intake of micronutrients is important considering that dietary habits may be affected by different lifestyle factors that could prevent women from achieving the increased nutritional demands of pregnancy. Such contribution was substantial in this study, in that without taking into account dietary intakes, the RDA for folic acid, vitamin D and iron were met, on average, by the study sample. Literature regarding dietary intakes of pregnant women suggests inadequacy of key micronutrients at some point of gestation or even throughout the whole pregnancy. As a result, we can predict that the contribution of key micronutrients from food sources would be low for folic acid and vitamin D. In that case, the use of NHPs becomes important to be able to meet current recommendations. On the other hand, based on the results of this study some micronutrient recommendations would not be met with NHPs alone. Calcium intake from NHPs was only one third of the current dietary recommendations meaning that food sources would be necessary to reach the total recommended intake of this mineral. Good sources of calcium are milk and dairy

products which seem to be some of the food products women are more likely to increase during pregnancy. Iron intake from food sources has also been reported inadequate in the pregnant population in different studies, and supplementation is encouraged. However, iron supplements may cause gastrointestinal discomfort in pregnant women and may be a reason for suspending their use as pregnancy progresses. Also, iron supplements are mainly in the non-heme form and intestinal absorption is low. In addition, iron absorption may also be impaired if high amounts of calcium are taken with it. The present study provided detailed information regarding the use of NHPs and their micronutrient contribution to daily intakes of pregnant women in each trimester of gestation, being able to describe nutrient intakes in Canadian population. As the majority of NHPs can be purchased without a medical prescription, the extent of use of NHPs should be carefully monitored by health professionals to avoid misuse. Excessive intakes and unregulated formulations may be of concern due to the possibility of teratogenic effects, when used in pregnancy. For a comprehensive nutritional assessment of pregnant women, both dietary and supplement intakes should be considered to develop more targeted counselling regarding use of NHPs.

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Appendix A
Ethics Approval

Re-Approval Form

Date:	February 14, 2011
Principal Investigator:	Catherine Field
Study Title:	Alberta Pregnancy Outcomes and Nutrition (APrON)
Approval Expiry Date:	February 13, 2012
Sponsor/Funding Agency:	AHFMR - Alberta Heritage Foundation for Medical Research

The Health Research Ethics Board - Biomedical Panel has reviewed the renewal request and file for this project and found it to be acceptable within the limitations of human experimentation.

The re-approval for the study as presented is valid for one year. It may be extended following completion of the annual renewal request. Beginning 45 days prior to expiration, you will receive notices that the study is about to expire. Once the study has expired you will have to resubmit. Any proposed changes to the study must be submitted to the HREB for approval prior to implementation.

All study-related documents should be retained, so as to be available to the HREB on request. They should be kept for the duration of the project and for at least five years following study completion.

Sincerely,

S.K.M. Kimber, MD, FRCPC
Chair, Health Research Ethics Board - Biomedical Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Appendix B
Study Information

MATERNAL INFORMATION SHEET

TITLE: Alberta Pregnancy Outcomes and Nutrition (APrON)[1]

INVESTIGATORS:, Catherine J. Field[2], Bonnie J. Kaplan,[1]Deborah Dewey[1], Rhonda Bell[2], Francois Bernier[1], Marja Cantell[1], Michael Eliasziw[1], Anna Farmer[2], Lisa Gagnon[1], Laksiri A. Goonewardene[2], Libbe Kooistra[1], Donna Manca[2], Linda McCargar[2], Maeve O'Beirne[1], Victor J.M. Pop[3], Nalini Singhal[1]

[1]University of Calgary, [2]University of Alberta, [3]University of Tilburg (The Netherlands)

Edmonton contact: **780-492-4667 or 780-240-1133**; Project Manager Dave Johnston at 403-955-2771

BACKGROUND AND PURPOSE

What we eat and drink tends to influence our health, both mental and physical. We would like to learn more about how nutrition influences pregnancy. Specifically we are interested in the role(s) of nutrition in women's health, baby's health, and the long term health and development of the child.

To help answer these questions, we are inviting you to join us in a study of 10,000 pregnant Albertan women and their children. The purpose of APrON is to learn how nutrition during pregnancy may affect women's physical and mental health, the health of the baby, and child health and development later on. The results of the study will be presented to parent groups, health professionals, food producers, day cares, and school boards. Our findings may improve the health and wellness of women and the health and development of children.

WHAT WOULD I HAVE TO DO?

Because this study will follow women through pregnancy and for several years after their babies are born, many measures will be collected over time:

1. Questionnaires. We are asking you to complete questionnaires at 8 time points:
    a. When you first agree to be in the study (which will hopefully be in your first trimester)
    b. Between 13-27 weeks of pregnancy (second trimester)
    c. Between 28-40+ weeks of pregnancy (third trimester)
    d. 2 - 3 months after your baby is born

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[1] The full title is the AHFMR Interdisciplinary Team Grant on the Impact of Maternal Nutrient Status during Pregnancy on Maternal Mental Health and Child Development.

e. Six months after your baby is born
f. Twelve months after your baby is born
g. Two years after your baby is born
h. Three years after your baby is born

The questionnaires will ask about *what you eat, how you feel, and what your pregnancy experience is like*. After your baby is born, the questionnaires will also ask you about *your baby's health, eating, crying, and behaviour.*

The questionnaires do not have to be done all at once; they can be completed in more than one sitting. Some of the questionnaires can be completed on: a) a secure University internet site, b) paper, or c) by telephone interview. In other words, *we will try to make these questionnaires fit into your busy life*. We estimate the questionnaires will take about two hours to complete at each of the eight time points.

2. Blood samples from you. You will be asked to provide a blood sample a total of 4 times during the study (3 times during pregnancy and once more, 3 months after your baby is born). The blood will allow us to look at the nutrient levels in your blood (e.g., vitamins, hormones, and measures of how they break down in your blood). Each blood sample is about 2.5 Tablespoons. On 2 occasions we will also ask you for a urine sample. The urine will be used to look at other nutrients. Each blood sample will take about 15 minutes.

3. Cheek swab or saliva sample from you. If there is no blood sample from you, we may ask you to rub a small brush inside your cheek (a cheek swab), or to provide a saliva (spit) sample. The cheek swab or saliva sample will be put in a plastic bag and returned to us in a pre-addressed and stamped, confidential envelope. The cheek swab or saliva sample will determine how genetics might relate to nutrition and health.

4. Body measurements. On 3 occasions during your pregnancy and at least one after birth we will measure your height and weight, arm and waist circumferences, and skin-fold thickness. We estimate this will take about 15 minutes.

5. Biological father questionnaires, and cheek swab or saliva sample. Around the middle of your pregnancy we will invite the biological father to participate in the study. The biological father is not required to take part. If you give us permission to contact him we will ask him to: a) complete a questionnaire during the pregnancy and after the delivery, and b) rub a small brush inside of his cheek or to provide a sample of his saliva. The sample and consent form are to be returned to us pre-addressed and stamped, confidential envelope. The cells from inside the cheek or the saliva will allow us to study whether the biological father's genetics relate to the child's health and development. We estimate this will take 5 minutes of his time.

6. Breast milk sample. If you are breast-feeding, we will ask you to provide a few drops of your breast milk about 3 months after your baby is born. We will examine the nutrient content of the breastmilk. A small piece of paper will be provided for this. The paper can be mailed back to us in a pre-addressed and stamped envelope or given to us when you meet with a member of our group. We estimate this will take about 5 minutes.

7. Blood sample from your baby. About 3 months after your baby is born we will ask if you are willing to allow us to take a small blood sample of about 1 teaspoon. Blood samples will be taken by a trained nurse or technician. As with your own blood sample, your baby's blood sample will allow us to look at the nutrient levels

in the blood (e.g., vitamins, and hormones). From the blood, we will also look at how genetics might relate to the nutrition and health of your baby. Your baby's blood sample should take about 15 minutes and it will be done when you are providing your own blood sample. Other options for getting samples from your baby may be available, including cheek swabs or saliva samples for genetics and heel pricks for nutrition.

8. Assessment of your child. When your child reaches three years of age, we may ask if we can assess his/her development, thinking, and learning ability. If you agree, a series of tests will be used to look at your child's learning and behavioural development. These tests will take about 1 ½ to 2 hours and will take place at a time of your choosing. Trained professionals will conduct these tests. You will be provided with verbal and written feedback about your child's performance.
9. Access to health records. We are asking for permission to access the health records for your pregnancy, delivery, and your child. Also, if you move and we lose touch with you, we ask your permission to contact Alberta Health and Wellness for your contact information so we can find out if you would like to continue your participation.

We estimate that the total time commitment for you and your child for study participation will be approximately 30-35 hours over the 4 year period.

WHAT ARE THE RISKS OF MY PARTICIPATING?

1. Blood samples: Blood will be taken from an arm vein by a person trained to draw blood (nurse, technician). Risks associated with blood draws include infection, bruising, blood clots, or inflammation. Steps will be taken to limit or avoid these risks.
2. Cheek swabs or saliva samples: A small brush will be used to rub against the inside of the cheek (cheek swab). A saliva sample will be provided by spitting on a piece of paper. The cheek swab or saliva sample poses no risk.
3. Heel pricks: If you do not wish your infant to have a needle for blood draws, a heel prick may be used instead. A few drops of blood will be collected on a piece of paper by pricking the infant's heel. Some minor bruising may occur and it may cause a small amount of pain to your infant.
4. All other measures: It is possible that answering questions about your health history or mental state may raise some feelings of sadness or distress. If at any point during the study you are having any difficulty with your mood or stress level, or feel you need some help with your mental health, please call your family doctor, the Distress Line at 780-482-4357 or the Edmonton Mental Health Clinic at 780-427-4444.

WILL I BENEFIT IF I TAKE PART?

If you agree to take part in this study there may or may not be a direct benefit to you. If your child takes part in the in-depth testing at age 3, we will provide you a summary of his/her results. If the testing identifies early development or learning problems, we would recommend that you discuss the results with your child's regular doctor. By participating

in APrON you will become a member of our team of participants and have access to a special website that will keep you updated on how the study is going.

DO I HAVE TO PARTICIPATE?

Taking part in this study is voluntary. You may choose not to answer some questions, not to take part in some tests, or to withdraw from the study at any time without affecting your health care. You can withdraw by contacting the Edmonton Project Coordinator at **780-492-4667 or 780-240-1133**.

Similarly, if you are unable to complete the study information in a suitable timeframe, the study staff may withdraw you.

WHAT ELSE DOES MY PARTICIPATION INVOLVE?

APrON will be following participants over a period of 3-4 years. At the end of the study, all samples (blood, cheek swabs) including DNA and all clinical data will be securely held by the researchers. It is possible more studies will develop from APrON. As a result, participants and their children may be followed beyond the first period of 3-4 years. You and your child may be asked to take part in these future studies. Access to the data and the samples will only be allowed for studies that have been approved by a Research Ethics Board. By signing below, you agree to have your information and left over samples examined in the future by other researchers. If at any point you decide you do not want researchers to keep your samples and data, by providing researchers with a written request you can always ask that your data and samples be destroyed.

I agree to have my own and my child's left over biological samples (blood and DNA) available to researchers for future studies which have been approved by a Research Ethics Board. No further consent will be needed from me in order for this to happen. I understand that these samples will only be released with non- identifying information. I can still request my samples be destroyed at any time

Signature: _____ *Date:* __*day* ___*month* _____*year*

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be paid for participating, but we also want to ensure that your participation does not cost you anything. We will reimburse any traveling or parking costs related to you taking part in this study.

WILL MY RECORDS BE KEPT PRIVATE?

The consent forms and any questionnaire information you provide will be kept in locked filing cabinets or scanned and shredded in a locked confidential bin. Your privacy and your identity will be kept confidential. The questionnaire and study information you provide will only be accessed by the researchers and will be kept locked in a secure research area. The study database will be stored on a computer drive protected by a password.

All samples will be stored in locked freezers in a secure research facility. The labeling of samples will be done with a study code number and will not identify you by name, health care number or initials.

By signing the consent form you give permission for the collection and use of your medical records. Even if you withdraw from the study, the medical information that is obtained from you for study purposes will not be destroyed, unless a written request is received from you.

All participants will receive regular newsletters, updating them on the progress of this study. At the end the whole study, or even at completion of parts of the study, we will send a summary to each participant. All the information contained in our summaries will be anonymous, and based on group data. Any report published as a result of this study will not identify you by name, address or any other personal information.

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

In the event that you suffer injury as a result of participating in this research, you will not be compensated in any way by the funder (AHFMR,) the University of Calgary, Calgary Health Region, the University of Alberta, Capital Health Region, Alberta Health Services, or the Researchers. You still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

If you have further questions related to this research, please contact:

Dr. Catherine Field (APrON Edmonton) **780- 492-4667**
Or
APrON Project Manager: Dave Johnston at 403-955-2771

If you have any concerns about any aspect of the study, please contact Health Research Ethics Board office, University of Alberta 780-492-9724.

Appendix C
Consent Form

MATERNAL CONSENT FORM

Title of Project: Alberta Pregnancy Outcomes and Nutrition (APrON)

Principal Investigator: Dr. Catherine Field Phone: 780-492-4667
Co-Investigators: Dr. Linda McCargar, Dr. Rhonda Bell, Dr. Anna Farmer, Dr. Donna Manca

Please circle your answers:

Do you understand that you have been asked to take part in a research study? Yes No

Have you received and read a copy of the attached Information Sheet? Yes No

Do you understand the benefits and risks involved in taking part in this research study? Yes No

Have you had an opportunity to ask questions and discuss this study with the researchers? Yes No

Do you understand that you can refuse to participate or withdraw from the study at any time? Yes No

You do not need to give a reason for withdrawing. Refusing to participate or withdrawing will not affect the medical care you receive.

Has the issue of confidentiality been explained to you? Yes No

Do you understand who will have access to your information? Yes No

Do you want the investigators to inform your family doctor that you are participating in this research study? Yes No

Doctor's name: _____

Do you agree to be contacted for future research studies and programs? Yes No

I agree to take part in this research study.

_____	_____	_____
Printed Name of Participant	Signature of Participant	Date

_____ _____ _____

Printed Name of Witness Signature of Witness Date

I believe that the person signing this form understands this study and voluntarily agrees to participate.

_____ _____ _____

Printed Name of Investigator Signature of Investigator Date

Appendix D
Supplement Intake Questionnaire

APrON – Supplement Intake Questionnaire

Participant ID:
Name:
Interviewer:

SECTION I. DIETARY SUPPLEMENTS

Instructions: The following questions are about the use of dietary supplements (vitamins, minerals, herbal / botanical remedies, teas, homeopathic medicines and animal derived products).[1]

1. Are you currently using or taking any **vitamins, minerals or other dietary supplements**? Include those products prescribed by a health professional and those that do not require a prescription.

- ❑ YES
- ❑ NO – Continue to Section II.
- ❑ Did not know – Continue to Section II.

2. When did you begin using dietary supplements?

- ❑ Before pregnancy. How long before? _____
- ❑ During pregnancy. Which trimester? _____

3. From the list below (show participant the list), please tell me **all** of the following **supplements** that you are currently taking.

Dietary Supplement	1st Visit Time Point: Date:		2nd Visit Time Point: Date:		3rd Visit Time Point: Date:		4th Visit Time Point: Date:	
Multivitamins:	✓	Dose / Frequency	✓	Dose / Frequency	✓	Dose / Frequency	✓	Dose / Frequency
Biquest Prenatal Multivitamins								
Centrum Materna								
Compliments Prenatal Multivitamins								
Equate Prenatal Multivitamins								
Exact Prenatal Vitamin and Mineral Supplement								
Generic Prenatal Multivitamins								

Health Balance Prenatal Multivitamins								
Kirkland Prenatal Multivitamins								
Dietary Supplement	**1st Visit** Time Point:		**2nd Visit** Time Point:		**3rd Visit** Time Point:		**4th Visit** Time Point:	
Multivitamins:	✓	Dose / Frequency	✓	Dose / Frequency	✓	Dose / Frequency	✓	Dose / Frequency
Life Brand Prenatal Multivitamins								
London Drugs Prenatal and Postpartum Multivitamins								
Materna								
Materna Me								
"No Name" Brand Prenatal Multivitamins								
Nutralife™ Multiple Vitamins And Minerals For Prenatal Women								
One a Day Women's Prenatal								
PregVit								
PregVit Folic 5								
President's Choice Prenatal Multivitamins								
SISU - Multi Expecting								
Western Family Prenatal Multivitamins								
Other (please specify brand and/or DIN / NHPN):								

Comments:

Dietary Supplement	1st Visit Time Point:		2nd Visit Time Point:		3rd Visit Time Point:		4th Visit Time Point:	
Single supplements:	✓	Dose / Frequency	✓	Dose / Frequency	✓	Dose / Frequency	✓	Dose / Frequency
B6 / Pyridoxine								
B-Complex								
Beta-Carotene								
Calcium / Calcium Supplements								
Coenzyme Q								
Compliments – Folic Acid								
Compliments – Vitamin D								
Fibre / Fiber Supplements								
Folic Acid / Folate								
Glucosamine								
Hydroxytryptophan (HTP)								
Iron								
Life Brand Prenatal Omega 3								
Life Brand Iron supplement								
Life Brand "Psyllum Husk" (fiber supplement)								
Niacin								
Phosphorous								
Selenium								
Vitamin A								
Vitamin C								
Vitamin D								
Vitamin E								
Zinc								
Other (please specify brand and/or DIN / NHPN):								

Comments:

4. From the list below (show participant the list), please tell me all of the following **herbal/ botanical** or **animal derived** supplements that you are currently taking.

Dietary Supplement	**1st Visit** Time Point:		**2nd Visit** Time Point:		**3rd Visit** Time Point:		**4th Visit** Time Point:	
Herbal supplements:	✓	Dose / Frequency / Place where they bought them	✓	Dose / Frequency / Place where they bought them	✓	Dose / Frequency / Place where they bought them	✓	Dose / Frequency / Place where they bought them
Aloe Vera								
Astragalus								
Bilberry								
Black Cohosh								
Black Elderberry								
Blue Cohosh								
Brewer's Yeast								
Cascara Sagrada								
Castor Oil								
Cat's Claw								
Cayenne								
Chamomile								
Chinese Herbs								
Cinammon								
Cod Liver Oil								
Cold FX								
Cranberry								
Dong Kuai (Tangkwei)								
Dried Cherry								
Echinacea								
Ephedra								
Evening Primrose Oil								

Dietary Supplement	1st Visit		2nd Visit		3rd Visit		4th Visit	
Herbal supplements:	✓	Dose / Frequency / Place where they bought them	✓	Dose / Frequency / Place where they bought them	✓	Dose / Frequency / Place where they bought them	✓	Dose / Frequency / Place where they bought them
Fish Oil (fatty acids)								
Feverfew								
Flaxseed Oil								
Garlic								
Ginger								
Ginko Biloba								
Ginseng (American or Asian)								
Goldenseal								
Grapeseed Extract								
Horsetail								
Kava, Kava								
Milk Thistle								
Peppermint								
Pregnancy Tea								
Pumpkin Seeds								
Raspberry Leaf								
Saw Palmetto								
Siberian Ginseng								
Slippery Elm								
St. John's Wort								
Valerian								
Homeopathic Remedies (please specify):								

Other (please specify brand and/or DIN / NHPN):								

Comments:

Finally, may I see the containers, bottles, labels or bags for **all** the prescription and nonprescription vitamins, minerals, and dietary supplements that you are currently using?

In case you do not have it with you at the moment, would you bring **all** of them to your next appointment?

SECTION II. WATER INTAKE.

The following questions are about your everyday water intake.

1. On a daily basis, which types of water do you usually drink? And what is the average intake (glasses/day) from the mentioned source(s)? Please check all that apply. 1 glass = 250 ml. / 8 ounces.

Sources	1st Visit *Time Point:*		2nd Visit *Time Point:*		3rd Visit *Time Point:*		4th Visit *Time Point:*	
	✓	Intake	✓	Intake	✓	Intake	✓	Intake
Bottled water								
Sparkling water								
Tap water								
Tap water (with filter)								
Other(s) please specify:								

References

1 Natural Health Products System Standard Terminology Guide Health Canada November 2008 Version 1 0

2 APrON Supplement Intake Questionnaire was adapted from Health Canada and Statistics Canada - "Canadian Community Health Survey - Nutrition (CCHS)" 2004, NHANES - "Dietary Supplements and Prescription Medication Survey" 2005-2006, and "The Tomorrow Project" 2006 questionnaires

Appendix E
Herbal Products reported by APrON participants

Herbal products reported by APrON participants during pregnancy[1].			
Herbal Product (daily intake)	**First Trimester (n=136)**	**Second Trimester (n= 575)**	**Third Trimester (n=516)**
TEAS			
Pregnancy teas	1	4	4
Green tea	1	4	2
Herbal tea	0	2	1
Peppermint tea	3	9	6
Chamomile tea	0	2	0
Black loose-leaf tea	0	4	0
Acai berry tea	0	1	1
Figure 8 Caffeine Free Detox tea	0	1	0
Green+	0	2	0
Youth Juice	0	1	0
OILS			
Ground Flaxseed / Flaxseed oil	1	2	2
Hempseed oil	1	1	1
Oil of Oregano 75-85% Carvacrol	0	1	0
Canola Oil Capsules	0	1	1
Efamol Evening Primrose Oil	1	1	0
PILLS			
Garlic pills	0	3	3
Calms Forté	0	1	0
Complete Digestive Enzymes	0	1	1
Estrosense	1	0	0
Oscillococcinum	0	1	1
Mikei Red Reishi Mushroom Essence	1	1	0
Premium Chlorella	0	1	1

Table 14.
Herbal products reported by APrON participants during pregnancy (Cont'd)

Echinacea	2	2	0
Cranberry Extract	0	2	2
LEAVES / ROOTS			
Raspberry Leaves	0	2	5
Ginger (tea or root)	2	9	0
Chinese herbs	1	2	1
Macaroot	0	1	1
Stingy Nettle	0	1	2
SEEDS			
Pumpkin seeds	0	1	1
POWDERS			
Perfect Food Super Formula	0	1	0
Herbal Aloe Powder Drink Mix	0	1	1
Mucil-Ace (natural fibre laxative)	1	2	1
Hemp protein	0	2	1
Soy Lecithin	0	0	1

[1] As reported by participant as daily intake in each visit.