Knowledge, Attitude and Practice of Physicians Regarding Periconceptional Folic Acid

Liana Arielle Mida

Interdisciplinary School of Health Sciences

Faculty of Health Sciences

University of Ottawa, Ottawa, ON

Under the supervision of Prof. Bénédicte Fontaine-Bisson, RD, PhD

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Abstract

Background Expert guidelines recommend low-risk women to consume a daily multivitamin supplement containing 400 µg of folic acid (FA) to prevent the occurrence of neural tube defects. This study assessed the knowledge, attitude and practice of physicians regarding FA recommendations, status and health outcomes during pregnancy since physicians play an essential role in promoting appropriate FA intake.

Methods A cross-sectional survey of a sample of physicians practicing in the National Capital Region was self-administered in 2018-2019.

Results Approximately 70% of physicians were not familiar with the most recent guidelines and 55% of them most often recommend a 1000 µg-FA supplement. A high level of willingness to recommend a supplement containing 400 µg-FA was reported by almost all physicians.

Conclusions While most physicians would not feel comfortable recommending a supplement that is not in line with the most recent evidence-based guidelines, educational programs targeted to physicians are needed to improve their knowledge, attitude and practice.

Keywords: Attitude; Folic Acid; Knowledge; Physicians; Practice; Pregnancy

Résumé

Contexte Les lignes directrices des experts recommandent aux femmes à faible risque de consommer chaque jour un supplément de multivitamines contenant 400 µg d'acide folique (AF), afin de prévenir le développement d'anomalies du tube neural. Cette étude a évalué les connaissances, attitudes et pratiques des médecins en ce qui concerne les recommandations, le statut et les issues de santé associées à l'AF pendant la grossesse puisque ces derniers jouent un rôle essentiel dans la promotion d'une consommation appropriée d'AF.

Méthodes Une enquête transversale auprès d'un échantillon de médecins exerçant dans la région de la capitale nationale a été autoadministrée en 2018-2019.

Résultats Environ 70% des médecins ne connaissaient pas les lignes directrices les plus récentes et 55% d'entre eux recommandent le plus souvent un supplément de 1000 µg de AF. Presque tous les médecins ont souligné un fort désir de recommander un supplément contenant 400 µg d'AF.

Conclusion Bien que la plupart des médecins ne sont pas à l'aise de recommandation un supplément qui n'est pas conforme aux plus récentes lignes directrices fondées sur des données probantes, des programmes d'éducation ciblés aux médecins sont nécessaires pour améliorer leurs connaissances, attitudes et pratiques.

Mots-clés: Attitude; Acide folique; Connaissance; Médecins; Pratique; Grossesse

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List of Abbreviations

5-MTHF	5-methyltetrahydrofolate
AI	adequate intake
BMI	body mass index
CpG	cytosine-guanosine
DFE	dietary folate equivalent
DRI	dietary reference intakes
EAR	estimated average requirement
FA	folic acid
FAA	folic acid- antagonist
GDM	gestational diabetes mellitus
MES	maternity experience survey
MTHFR	methylenetetrahydrofolate reductase
nmol/L	nanomoles per litre
NTD	neural tube defect
OB-GYN	obstetrician-gynaecologist
PVS	prenatal vitamin/mineral supplements
RBC	red blood cell
RCT	randomized control trial
RDA	recommended dietary allowance
REB	research ethics board
SAS	statistical analysis software
SES	socioeconomic status
SOGC	Society of Obstetricians and Gynaecologists of Canada
THF	tetrahydrofolate

UL	tolerable upper intake level
WCBA	women of childbearing age
WHO	world health organisation

Outline of Thesis

The following thesis is written in a "thesis by article" format, consisting of five chapters.

Chapter 1: Theoretical foundations on folate metabolism and requirements, recommendations for pregnancy and a description of the current folate status of the Canadian population are thoroughly reviewed in this chapter. Additionally, nutritionally-induced epigenetic modifications (i.e. DNA methylation) capable of affecting fetal health outcomes are presented.

Chapter 2: The rationale for conducting this study follows, including the specific research objectives and hypothesis.

Chapter 3: The methodology is described in the third chapter. This section includes an overview of the study design, methods and tools used for data collection as well as the analytic approach.

Chapter 4: The article aims to assess the knowledge, attitude and practice of physicians regarding periconceptional folic acid. It examines how the knowledge, attitude and practice of physicians can contribute in mitigating the existing misalignment between current guideline recommendations and the folic acid content in prenatal vitamin/mineral supplements on the Canadian market. This article has been formatted for submission to *Preventive Medicine* and conforms to the standard of that peer-review journal.

Chapter 5: A discussion section interpreting the results in light of the research question is presented. In addition, this chapter offers reflections on the significance and implications of the study as well as future directions for research in this area.

Chapter 1: Review of the literature

The maternal diet during pregnancy is important because intrauterine nutritional and environmental exposures may have adverse effects on lifelong organ structure and function, which ultimately influence offspring health, development and disease risk. Folate is an essential nutrient that is particularly important due to its vital role in biosynthetic pathways. Demands for folate increase during periods of rapid growth such as pregnancy to support the development of the fetus. Adequate intakes of folate are important to contribute toward optimal long-term health outcomes.

1.1 Folate and Folic Acid

Folate, the naturally occurring form of vitamin B9, is a generic term for chemically related compounds that share a common pteroylglutamic acid (or "folic acid") structure (1,2). It is a complex, water-soluble, B-vitamin that is considered to be one of the 13 essential vitamins as it cannot be synthesized de novo by the body and thus, must be obtained from either diet or supplementation (3). Rich sources of naturally occurring folate include legumes (e.g., beans and lentils), leafy green vegetables (e.g., romaine lettuce, spinach and mustard greens) and dark green vegetables (e.g., broccoli, brussel sprouts and peas) (4,5). Pteroylglutamic acid, or folic acid (FA) is the synthetic, most stable form of folate and thus, the form most commonly used in dietary supplements and as a fortificant in foods (2,6) .

Bioavailability is a function of absorptive and postabsorptive processes and is defined as the proportion of a nutrient ingested that becomes available to the body for metabolic processes or storage (7). Natural food folates found in a typical diet are rather unstable molecules, have poor bioavailability and food processing renders a reduced vitamin activity (7). This is because dietary folate is primarily present in the reduced, more labile polyglutamated form with methyl or formyl as the one-carbon substitution (8). The bioavailability of dietary folate may be hampered by the polyglutamate chain to which most of the natural folate is attached; therefore, folic acid, the fully oxidized and monoglutamate form of folate is easily reduced to tetrahydrofolate and able to participate in metabolic reactions (7,8).

Folate bioavailability from different foods is considered to be dependent on a variety of factors, including the food matrix, the intestinal deconjugation of polyglutamyl folates, the instability of certain labile folates during digestion and the presence of certain dietary constituents that may enhance folate stability during digestion (7–9). It is widely recognized that folic acid possesses greater bioavailability than food folate, however, there is conflicting evidence as to whether the extent of conjugation of polyglutamyl folate (in the absence of specific inhibitors of deconjugation in certain foods) is a limiting factor in folate bioavailability (7). Furthermore, the poor stability of food folates (particularly green vegetables) causes typical conditions of cooking and preparation of foods to substantially reduce the amount of vitamin ingested and thereby be an additional factor limiting the ability of food folates to enhance folate status (7,8,10). Folate contains one to six additional glutamate molecules joined in a peptide linkage to the γ-carboxyl of glutamate, preventing it from being absorbed by the body (11). When folic acid, the monoglutamate form of folate, is taken up by enterocytes, it is easily hydrolyzed into 5-methyltetrahydrofolate (5-MTHF), the metabolically active form of circulating folate (8,12,13).

It is widely received that food folate bioavailability is lower than that of folic acid, however, the extent of their bioequivalence remains uncertain and shows great variation, ranging between 30 and 98%, depending on the methodological approach used (7,8,14,15). Estimates suggest that approximately 50% of the folate naturally found in food is absorbed; whereas the bioavailability of FA is almost double that of folate due to the unnecessary requirement for enzymatic removal of excess glutamates (15,16). When taken with food, synthetic folic acid is approximately 85% bioavailable, and up to 100% when supplemental folic acid is taken in a fasted state (16). To account for differences in folate and folic acid bioavailability, Dietary Folate Equivalent (DFE) was created, with 1 µg DFE being equivalent to 1 µg of food folate or 0.6 µg of folic acid consumed with food or 0.5 µg folic acid consumed in a fasted state (16).

1.1.1 Folate One-Carbon Metabolism

Tetrahydrofolate (THF) polyglutamates are a family of cofactors that carry and chemically activate one-carbon units for biosynthesis. THF-mediated, or folate-mediated one-carbon metabolism is a metabolic network of interdependent biosynthetic pathways that are compartmentalized in the cytoplasm, mitochondria and nucleus (17).

Five major one-carbon transfer reactions occur within the cell: conversion of serine to glycine, catabolism of histidine, and synthesis of thymidylate, methionine, and purine (Figure 1). These reactions take place through various electron transfer steps facilitated by specific enzyme systems and coenzymes such as flavin adenine dinucleotide (FADH2) and nicotinamide adenine dinucleotide (NADPH) (12). Folate coenzymes are best known for their role as acceptors and donors of one-carbon moieties in reactions involving nucleotide and amino acid metabolism; these reactions are known as folate-mediated one-carbon metabolism (18). There are many critical cellular pathways dependent on folate derivatives to ensure proper DNA, RNA, and protein methylation as well as DNA and RNA biosynthesis and repair (Figure 1) (12,18,19). Folate's metabolic role is to carry one-carbon units that exist at various levels of oxidation and thus, folate can be a limiting factor in all these reactions (12,18). Folate-dependent metabolic pathways are compartmentalized in the cell where the mitochondria houses and sequesters approximately 40% of total cellular folate (17). A primary function of mitochondrial one-carbon metabolism is to generate one-carbon units in the form of formate for cytoplasmic one-carbon metabolism (18,20). In the mitochondria, amino acids serine, glycine, dimethylglycine, and sarcosine are catabolized to produce formaldehyde, which is condensed with THF to generate methylene-THF. The activated formaldehyde of methylene-THF is oxidized, forming 10-formyl-THF, which serves to formylate MET-tRNA for mitochondrial protein synthesis, or alternatively, 10-formyl-THF is hydrolyzed to THF and formate, which enter the cytoplasm (18,20). Cytoplasmic one-carbon metabolism uses mitochondrially derived formate for nucleotide biosynthesis and for the remethylation of homocysteine to methionine.

Folate-mediated one-carbon metabolism in the cytoplasm includes a set of interdependent biosynthetic pathways that catalyze the de novo synthesis of purines, thymidylate, and the remethylation of homocysteine to methionine (18). Methionine is activated by adenosine triphosphate (ATP) and adenosylmethyltransferase and acts as a precursor for the synthesis of S-adenosyl-methionine (SAM) (18,20,21). Subsequently, SAM functions as a cofactor and universal methyl group donor for numerous methylation reactions, including the methylation of DNA, RNA, neurotransmitters and other small molecules, phospholipids, and proteins including histones (12,17,18,20). Despite their specialized functions, all the folate-dependent pathways and intracellular compartments are interdependent and interrelated. In the absence of sufficient methyl donors, homocysteine, produced from the breakdown of methionine, increases and cannot be remethylated to produce methionine (18,22). Consequently, homocysteine levels are influenced by intake of dietary methyl donors and cofactors involved in the one-carbon metabolism process. Acting as a methyl donor in one-carbon metabolism, folate derivatives are critical. Therefore, adequate folate intake during periods of rapid cellular replication, such as pregnancy, is essential to support fetal growth and development; most notably, closure of the neural tube.

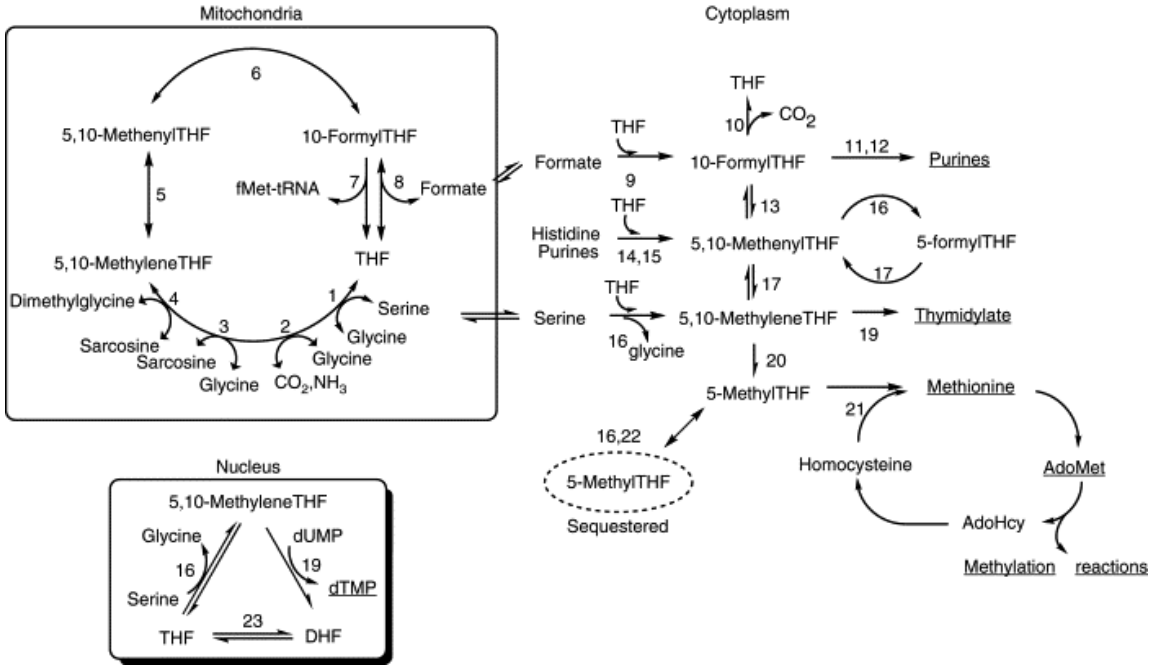

Figure 1. Folate-mediated 1-carbon metabolism Compartmentation of folate-mediated one-carbon metabolism in the cytoplasm, mitochondria and nucleus. One-carbon metabolism in the cytoplasm is required for the *de novo* synthesis of purines and thymidylate and the remethylation of homocysteine to methionine. One-carbon metabolism in the mitochondria is the primary generating source of one-carbon units for cytoplasmic one-carbon metabolism. One-carbon metabolism in the nucleus synthesizes dTMP from dUMP and serine. 1, Mitochondrial serine hydroxymethyltransferase; 2, Aminomethyltransferase; 3, Sarcosine dehydrogenase; 4, Dimethylglycine dehydrogense; 5, 5,10-Methylenetetrahydrofolate dehydrogenase (NAD-dependent); 6, 5,10-Methenyltetrahydrofolate cyclohydrolase; 7, Methionyl-tRNA formyltransferase; 8, 10-Formyltetrahydrofolate synthetase; 9, 10-Formyltetrahydrofolate synthetase; 10, 10-Formyltetrahydofolate dehydrogenase; 11 and 12, Phosphoribosylglycinamide formyltransferase and Phosphoribosylaminoimidazolecarboxamide formyltransferase; 13, 5,10-Methenyltetrahydrofolate cyclohydrolase; 14 and 15, Glycine formiminotransferase/formimidoyltetrahydrofolate cyclodeaminase and Glutamate formiminotransferase/formimidoyltetrahydrofolate cyclodeaminase; 16, Cytoplasmic serine hydroxymethyltransferase; 17, Methenyltetrahydrofolate synthetase; 18, 5,10 Methylenetetrahydrofolate dehydrogenase (NADP-dependent); 19, Thymidylate synthase; 20, Methylenetetrahydrofolate reductase; 21, Methionine synthase; 22, Glycine N-methyltransferase; 23, Dihydrofolate reductase. **(Source for reuse: Fox and Stover, 2008 Chapter 1)**

1.1.2 Neural Tube Defects (NTDs)

The majority of structural birth defects result from a complex interplay between environmental exposures, lifestyle factors, and genetic and epigenetic processes (23). Neural tube defects (NTDs) are a multifactorial group of heterogeneous anomalies of the central nervous system characterized by incomplete closure of the neural tube during embryogenesis (14,24). They are one of the most common,

and critical types of congenital disorders associated with substantial mortality, morbidity, and long-term disability (14,24–26). The abnormal development and closure of the neural tube, resulting in damage to the exposed underlying neural tissue, is completed within 28 days after conception (3^{rd}-4^{th} weeks), before many women are aware that they are pregnant (14,18,24,26). Anencephaly and spina bifida are the two most common and severe types of NTDs, affecting the brain and spinal cord, respectively (18,23,24). Anencephaly is fatal where all children are stillborn or die shortly after birth; only 25% of babies live up to 10 days, while 50% have a life expectancy of between a few minutes and one day (24,27). Many infants with spina bifida are now likely to survive as a result of extensive medical and surgical care that has advanced greatly; however, not without severe, life-long disabilities and increased risk for psychosocial maladjustment (18,24).

Neural tube defects are a major, yet preventable public health concern and burden (28). They are an important health issue because of their detrimental impact on the health and wellbeing of Canadian infants, children and their families. Worldwide, it is estimated that approximately 300,000 to 400,000 neonates are affetected with NTDs each year, becoming a major cause of neonatal morbidity and mortality (28–30). Every year in Canada, approximately 1 in every 25 babies is diagnosed with one or more congenital anomalies (e.g. Down syndrome, orofacial clefts and congenital heart defects) with neural tube defects having a prevalence rate of 1 out of every 2,500 births (30).

Between 1998 and 2009, the national prevalence rate of congenital anomalies decreased from 451 to 385 per 10 000 total births with substantial reductions in neural tube defect rates as well (19-54%) (8,30,31). Fortification of flour, which began in early 1997 and gradually became widespread, is a plausible explanation for the timing, shape and magnitude of the decrease in NTD prevalence observed (32). In 2006, the March of Dimes Global Report on Birth Defects published a global estimate of 324,000 births (2.4 per 1000 live births) affected by NTDs in 2001, contributing to over 2.3 million disability-adjusted life years (33). Using updated input parameters yielded a global estimate of 260,100 NTD-affected

pregnancies in 2015.(25). The improved rates can likely be attributed to three main factors: (1) increased prenatal diagnosis and subsequent pregnancy termination; (2) mandatory folic acid fortification of food; and (3) changes in health behaviours and practices such as a reduction in tobacco smoking in pregnancy (18,24,27). Despite global and national decreases in the overall prevalence rate, congenital malformations and deformations remain the number one leading cause of infant deaths in Canada, with 375 infant deaths in 2017 (34).

Over the last 30 years, public health initiatives to increase the awareness and prevention of birth defects have focused on the intake of folic acid during the periconceptional period. There exists a historical link between lower socioeconomic status (SES) and higher risk of birth defects, which led researchers to examine, and later confirm the involvement of nutritional factors and ultimately, folate in NTDs (23). Although the exact mechanisms remained unclear at that time, the longstanding relationship between folate deficiency and NTD occurrence was hypothesized as early as 1965 (35).

Initially, experimental studies found FA-antagonists (FAA) to be highly teratogenic in pregnant rats producing a variety of congenital anomalies (36). In 1952, Thiersch used aminopterin, a FAA, for therapeutic abortions and the relationship was confirmed in humans as well (37–39). Eventually, in 1964, Hibbard suggested that folate-deficiency may also have a role in NTDs after reporting a higher rate of congenital abnormalities (3.0%) in infants of folate-deficient mothers in comparison to the control group (1.6%) (35). A number of studies suggested that folic acid plays a role in reducing the risk of NTDs (40–42) which led to increased investigations regarding the relationship between human embryopathy and folate deficiency (43). In 1976, a breakthrough study by Smithells et al. officially attributed undernutrition as a triggering environmental factor in the origin of NTDs, specifically finding that babies born to folate-deficient mothers are more likely to have NTDs (44). Smithells et al. published findings from the first intervention study, testing the effect of diet supplemented with a multivitamin containing 0.36 mg FA for the reduction of recurrent NTDs (45). The risk of recurrence in supplemented women was about one-

seventh that in unsupplemented women (46). The lower recurrence rate in supplemented women was unlikely to have arisen by chance. These results propelled a study that confirmed FA to be the component in the multivitamin bearing protective effect, unlike the other seven vitamins present in the formulation (47).

The Medical Research Council in the UK organized a multicenter randomized control trial (RCT) to determine the efficacy of FA supplementation in the prevention of recurrent NTDs (47). The RCT found that a 4 mg dose of periconceptional folic acid, alone, was able to reduce at least 72% of NTDs in the second child (47). The year following the success in secondary prevention, Czeizel and Dudas' Hungarian RCTs demonstrated that a daily prenatal vitamin supplement (PVS) containing 800 µg of FA is a significantly effective strategy in preventing first NTD occurrence (48). Other studies using doses as low as 0.36 mg (40) to 0.4 mg (49) have also demonstrated daily FA supplementation to be more than 90% effective in the primary prevention of NTDs. The high-level evidence that resulted from the aforementioned RCTs resonated. Consequently, periconceptional supplementation with 400 µg of FA is recommended internationally to all women capable of becoming pregnant for the primary prevention of neural tube defects, such as spina bifida and anencephaly (4,16,29).

Although the benefit of reducing the risk of NTDs through FA supplementation before pregnancy and during the early weeks of gestation is well established, such an intervention only targets women planning a pregnancy or recently pregnant. However, approximately half of pregnancies in Canada are estimated to be unplanned (50). To compound the problem, the Society of Obstetricians and Gynaecologists of Canada (SOGC) surveyed more than 3200 Canadian women aged 15-50 regarding their awareness and use of contraceptive methods. The SOGC first conducted this survey in 2006 and again in 2016, finding that more women of childbearing age (WCBA) are relying on less effective methods of birth control and are using them less consistently than they did a decade ago (51). Furthermore, contraceptive choice in Canada continues to be framed, as well as limited by our social class, culture and religion (52).

1.1.3 Food Fortification

There are a number of public health strategies to ensure appropriate micronutrient consumption in WCBA, however, public awareness and mass media campaigns have only been somewhat effective in increasing knowledge about the importance of FA, while overall periconceptional FA supplement use continues to be low, especially among high-risk population groups (53–55). Fortification, the process of increasing the level of nutrients normally present within an appropriate food vehicle is a cost effective nutrition intervention strategy to reach large numbers of the population (18). It is especially important for women with lower levels of education and income who generally have difficulties buying more expensive folate-rich foods or PNVs and who have unplanned pregnancies more frequently (54,55). Fortification specifically targets to increase all WCBA's folate status because neural tube closer occurs during the critical window in which intervention is already necessary. Mandatory folic acid fortification programs have been implemented in many countries to improve the folate status of WCBA helping to mitigate issues of high costs, distribution problems and low compliance associated with supplement use, to ultimately prevent disease (53,56).

1.2 Folic Acid Supplementation During Pregnancy

Today, 82 countries, including Canada, have legislation to mandate nationwide mandatory fortification programs in which at least one industrially milled cereal grain product (wheat flour, maize, or rice) is fortified with folic acid (53,57). On November 11, 1998, Canada implemented mandatory FA fortification for all white flour, enriched pasta and cornmeal with the goal to increase FA intake among WCBA by 30-70% without posing a risk to the general public (58). White flour, cornmeal and other grain products are fortified at 150 µg of folic acid per 100 g and pasta is fortified at 200 to 270 µg of folic acid per 100 g to account for possible cooking losses (18,58). Higher levels of fortification were not adopted in order to respect the recommended daily upper intake level (UL) of 1000 µg for adults (16). The impact of implementing food fortification with FA was revealed in a retrospective study conducted by De Wals et

al. to assess changes in the prevalence of NTDs in Canada before and after food fortification with FA was implemented. The prevalence of NTDs decreased significantly from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period, marking a 46% reduction (31). Likewise, fortification with folic acid has proven to have had a major impact on NTD prevalence in all countries where it has been implemented and reported (26,59). Despite the fortification programs' success, government and health organization bodies additionally recommend periconceptional multivitamin supplementation to ensure appropriate FA intake regardless of a woman's NTD risk status.

1.2.1 Dietary Reference Intakes (DRIs)

Dietary Reference Intakes (DRIs) are a comprehensive set of nutrient reference values developed by the Food and Nutrition Board of the Institute of Medicine, to help plan and assess nutrient intakes of healthy American and Canadian populations. Contingent on available data, each nutrient has a set of DRIs including an Estimated Average Requirement (EAR) and either a Recommended Dietary Allowance (RDA) or an Adequate Intake (AI) indicating the recommended daily nutrient intake (16). The EAR is the median daily intake value that is estimated to meet the physiological requirement, as defined by the specified indicator of adequacy, in fifty percent of healthy individuals in a life stage or gender group (defined by biological sex, age and life events such as pregnancy and/or lactation). The EAR is used to calculate the RDA (RDA = EAR + $2SD_{EAR}$), which refers to the average daily nutrient intake goal that is expected to sufficiently meet the requirements of 97-98% of healthy individuals in a particular sex or life-stage group. The AI is established when there is insufficient scientific evidence to determine an EAR and thus the RDA values. The AI is a recommended average daily nutrient intake level, based on experimentally derived intake levels or approximations of observed mean nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate (60). Lastly, using the Risk Assessment Model, a tolerable upper intake level has been determined as the highest mean daily intake or nutrient concentration threshold that is unlikely to pose any adverse health risk to the general population, and above which may

result in adverse health effects (16). The established UL for folic acid was based on case reports from the 1940s suggesting that high-dosed FA intake (≥5 mg), used to treat patients with pernicious anemia, had the potential to precipitate neuropathy. Recently, newly obtained historical documents from the 1940s reveal a lack of evidence to support the finding that FA fortification has the potential to cause neurological damage in individuals with vitamin B12 deficiency and that perhaps the current UL should be reconsidered (61). In addition to planning and assessing diets, these DRI values are used to determine the risk of inadequacy, adequacy and excessive intake in a population. Since many chronic degenerative diseases and developmental abnormalities may not be detectable for significant periods of time, it is quite possible that individuals who have increased risk due to diet may not be identifiable. As a result, long-term intake may be more or less than that which is recommended in order to decrease risk of the disease state.

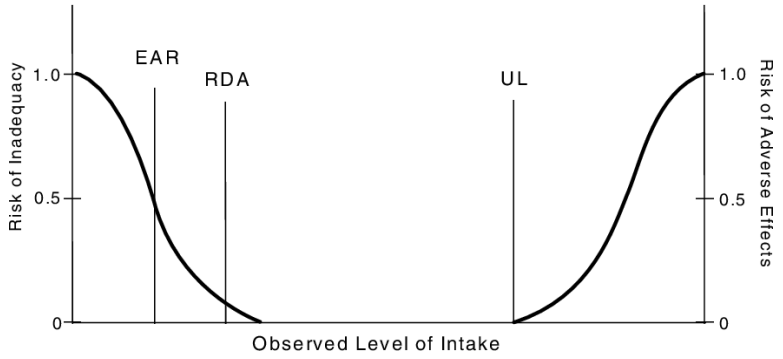

Figure 2. Dietary Reference Intake Reference Values for Vitamins, "Folate"

The Estimated Average Requirement (EAR) is the intake at which the risk of inadequacy is 50% to an individual. The Recommended Dietary Allowance (RDA) is the intake at which the risk of inadequacy is very small—only 2% to 3%. The Adequate Intake (AI) does not bear a consistent relationship to the EAR or the RDA because it is set without being able to estimate the average requirement. It is assumed that the AI is at or above the RDA, if one could be calculated. At intakes between the RDA and the tolerable

upper intake level (UL), the risks of inadequacy and of excess are both close to zero (0). However, the risk of adverse effects may increase with intakes above the UL.

1.2.2 Recommendations

Pregnancy is associated with a marked increase in cell division and metabolic processes dependent on one-carbon transfer reactions and thus, folate coenzymes. As mentioned in Section 1.1.1, folate is essentially involved in the transfer of one-carbon units obtained from various donor substrates to support the biosynthetic pathways of several molecules such as purine and pyrimidine nucleotides (18,48). Folate requirements during pregnancy increase to ensure normal cell division and metabolism associated with rapid uterine enlargement, increased maternal erythrocyte count and placental and fetal development (62,63).

Over the past few decades, evidence has amounted to confirm that periconceptional administration of multivitamin supplements or a FA supplement alone prevents the occurrence (48) and recurrence (47) of NTDs; ensuring that the embryonic structure ultimately develops into the brain and spinal cord. Internationally, periconceptional supplementation with 400 µg of FA is recommended (4,16,29). The Public Health Agency of Canada, Health Canada and the SOGC all recommend a daily multivitamin supplement containing 400 µg of folic acid for the primary prevention of neural tube defects among low-risk women from three months before conception, throughout pregnancy and throughout lactation (4,5,64). The World Health Organization (WHO) recommends all women, from the moment they begin trying to conceive until 12 weeks of gestation, to take a daily folic acid supplement containing 400 µg (29). Although there is agreement on the dose, globally, there exists a discrepancy in regard to the recommended duration between regulatory bodies. The association between FA supplementation and NTD risk has been studied over the past several decades, where studies have focused on FA intake during different stages from pre-pregnancy to the postnatal period. Subsequently, recommendations for the

period of intake vary between countries (ex. ranging from 1st trimester to breastfeeding period) depending on the evidence used to support their public health recommendations.

In 2015, the most recent SOGC evidence-based Clinical Practice Guideline was published in the *Journal of Obstetrics and Gynaecology Canada* and is regarded as the current national expert guideline (5). The SOGC recommends that women with a low risk for NTDs or other FA-sensitive congenital anomalies, and those who have a male partner with low NTD-risk, should consume a daily oral multivitamin supplement containing 400 µg of FA for at least 2 to 3 months before conception, throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues in addition to a diet of folate-rich foods (5). According to the SOGC, women with a moderate-risk for NTDs or other FA-sensitive congenital anomalies or a male partner with moderate risk require daily oral supplementation with a multivitamin containing 1000 µg of FA, beginning at least 3 months before conception. Women should continue this regime until 12 weeks' gestational age and should continue with 400-1000 µg of FA throughout pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues (5). The SOGC recommends women with a high-risk for an NTD, or a male partner with a personal history of NTDs or history of a previous NTD-pregnancy in either partner, to consume a daily oral supplement with 4000 µg FA for at least 3 months before conception and until 12 weeks' gestational age. From 12 weeks' gestational age, continuing throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should consist of a multivitamin with 400-1000 µg of FA (5).

Low-risk women are the most likely to consume too much folic acid due to the cumulative intake of dietary folate, FA-fortified staple foods and prenatal vitamin supplements (50,65). The well-established role of folic acid in preventing NTDs led to the fortification of all white flour, cornmeal and enriched pasta in Canada, providing an additional 100-200 µg FA per day to WCBA (described in Section 1.1.2) (66,67). Since the implementation of Canada's fortification program, the folate status has increased and the NTD

prevalence rate has decreased significantly, independent of consumption of additional folic acid supplements (31). However, with increased demands during pregnancy, folic acid supplementation is necessary due to the widespread under-provision of folate that is generally attributed to its poor bioavailability of natural food folates (7). Among non-supplement consuming Canadian women, it is estimated that <1% consume ≥0.4 mg of FA per day from dietary sources alone (65). This is why the need for supplements remains undeniable even in countries with mandatory grain fortification.

Plasma or serum folate and red blood cell (RBC) folate are used as reliable biomarkers of folate status and reflect changes in folate intakes (68). Serum folate is considered an indicator of recent folate intake and is likely the best indicator of bioavailability as the circulating form, reflecting the folate available to tissues (8). Conversely, red blood cell folate concentrations respond slowly to changes in folate intake and thus, RBC folate concentrations are useful to indicate long-term folate status (69). Colapinto et al. found that 22% of Canadian WCBA have sub-optimal blood serum folate concentrations for maximal NTD prevention (70). To promote prevention of NTDs, an optimal population-level threshold for RBC folate concentration of >906 nmol/L was set by the WHO in 2015, while the cut-off for preventing folate deficiency is 305 nmol/L (71,72).

1.2.3 Shifting Folate Status of Canadians

There has been a dramatic shift in the folate status of Canadians over the past 50 years. The 1970-1972 Nutrition Canada Survey reported the nutritional status of Canadians and at that time, 50% of Canadian WCBA had serum levels indicative of being at moderate or high-risk for folate deficiency (73). Colapinto et al. assessed the folate status of a nationally representative sample of Canadians, including a subset of WCBA. Using blood folate values from the 2007-2009 Canadian Health Measures Survey, this study was the first to assess the nationally representative sample post fortification (70). Presently, folate deficiency (RBC folate <305nmol/L) is virtually nonexistent in the population as a whole, which is likely

due to the mandated fortification program introduced in 1998 (70,74). WCBA were the target of the FA intervention; however, this strategy universally increased folic acid intake in Canada and thus, folate status of the entire population (75). Consequently, approximately half of the total female Canadian population have RBC folate concentrations that meet or exceed the high-concentration cut-off (1360 nmol/L), which will include a majority of women of childbearing age (WCBA) (70). Another large-scale Canadian study (n=1008), found that approximately 75% of women not consuming supplements had protective blood folate concentrations ≥ 906 nmol/L (67). The increased shift in folate intake among WCBA reflects the repercussions of food fortification and highly dosed prenatal vitamin supplements.

Prenatal multivitamin supplementation, in addition to diet, leads to micronutrient intake levels that exceed the RDA (76). In Canada, over the counter FA supplements marketed to pregnant women contain ≥400 µg of FA, while supplements containing >1000 µg of FA are available by prescription only (77). Despite the recommendations and expert guidelines, the vast majority of PVS on the Canadian market contain approximately 1000 µg of folic acid, preventing health care professionals and women from following public health recommendations. Consequently, high intakes of supplemental folic acid, coupled with staple FA-fortified foods, has resulted in intake levels that exceed the UL. Furthermore, RBC folate concentrations among pregnant women and women of childbearing age across the country are highly elevated (70,78–82).

In 2006-2007, the Canadian Maternity Experiences Survey (MES) surveyed women about their experiences and practices before and during pregnancy until a few months after birth (64). The MES revealed that 78% of Canadian women knew that taking folic acid before conception could help protect their baby from NTDs. Although 89% of women took supplements during the first three months of pregnancy, only 58% reported taking a FA-containing supplement before pregnancy (64). When comparing the literature, it is clear that North American women, are consuming high levels of FA after supplementation. This is especially true for those of higher socioeconomic status, and findings from the

MES confirm this. Social factors such as education, economic status, age and planning for pregnancy resulted in different levels of FA knowledge and use (64). Overall, however, mandatory fortification and increased adherence with periconceptional supplement recommendations has resulted in the significant, and potentially concerning shifting of folate status in North America (65,70,83,84).

Concerns are particularly raised over pregnant supplement users since maternal nutrition can lead to permanent alterations of DNA methylation patterns in the developing fetus, alter gene expression and ultimately, these changes can be preserved over time and may lead to long-term consequences for offspring and/or maternal health (85).

1.2.4 Excessive folic acid intake among pregnant women

In a post-fortification era, with concern over a majority of widespread and available prenatal vitamin supplements containing 1000 µg of FA on average, many studies have examined dietary and supplemental intakes of FA in pregnant Canadian women. The Prenatal Health Project collected data from thousands of pregnant women (n=2019) in London, Ontario, showing that the mean daily intake of folate was 473 µg/day DFE from diet alone, which is lower than the RDA for pregnant women (600 µg/day DFE) (86). However, the total dietary intake of folate from both food and supplemental sources was 2148 µg/day DFE in the majority of women (86).

Likewise, the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort consisted of predominantly Caucasian women with high SES who were taking a supplement during pregnancy. However, Fayyaz et al. observed that 24% of the cohort had suboptimal RBC concentrations (<906 nmol/L) during the first trimester, which corresponds to only 36% of women who reported taking a FA supplement prior to pregnancy (79). Comparable findings of suboptimal folate concentration during early pregnancy were also observed in the Canadian Health Measures Survey and a study reporting on pregnant Ontarian women (70,87). On the other hand, the proportion of women with suboptimal RBC folate concentrations

in the APrON study decreased drastically from 24% during the first trimester, to 9% and 7% in the second and third trimesters, respectively. In fact, high RBC folate concentrations (>1360 nmol/L) were observed in half of the women during each pregnancy trimester, with a majority of women consuming FA at or above the UL (median daily intake = 1000 µg FA) (79).

In a similar fashion, the Prenatal Folic Acid Exposure on DNA Methylation (PREFORM) study was conducted on hundreds of pregnant women across Southern Ontario (n=364) and found that 41% of pregnant women had inadequate FA intake from diet alone, with dietary folate intakes below the EAR (80). Maternal RBC folate concentrations were 2417 nmol/L and 2793 nmol/L in early pregnancy and at delivery, respectively; while unmetabolized folic acid was detected in more than 90% of maternal and cord plasma samples (80). This is likely attributable to high intake levels of synthetic FA which must first be converted into active and coenzymatic tetrahydrofolate derivates. Accordingly, the body is saturated with different forms of circulating folate species.

The 3D Cohort Study consisted of 1533 pregnant women in Quebec, assessing dietary intakes from both food and supplements sources. The study showed that 70% of the women had folate intakes below the EAR from diet alone; however, when intake from both sources was considered, 87% of the women had total intakes above the UL for folic acid (81). Similarly, the ANGE project (n=79) (*Apports Nutritionnels Durant la GrossessE*) in Quebec reported that a majority of pregnant women used prenatal vitamin supplements throughout all three trimesters (86.1%, 84.8% and 78.5% in the first, second and third trimesters, respectively) (82). A high prevalence of inadequate folate intake was observed in all trimesters (58.2%, 60.8%, 68.4%) when food sources were considered alone; however, when food sources and dietary supplements were combined, 86-90% of women's total intakes of FA were above the UL (82).

Most women from Canadian pregnancy cohorts are of Caucasian descent with higher SES, with an older age at pregnancy and higher levels of education and income (80–83). Thus, they are more likely to

have better folic acid knowledge as well as comply with recommendations and use a FA-containing supplement (6,67,88–91). These studies found that a majority of Canadian women of higher SES and those residing in urban cities are compliant in taking a FA-containing supplement. However, these finding conflict with nationally representative data that reveals only 15-29% of Canadian WCBA are taking a supplement (65,92–94). This discrepancy is two fold; firstly, prenatal vitamin supplement usage is associated with ethnicity, education, maternal age, employment, and income. Secondly, once women are aware that they are pregnant, they are quick to begin supplementation (95). The ultimate goal is to ensure that every Canadian woman consumes an optimal amount of folic acid depending on individual NTD risk status. To do so, it is important to recognize that a large portion of the population may be at a higher risk of inadequate folic acid consumption, and therefore at a higher risk for NTDs (96–98). Nonetheless, the literature above demonstrates that intake levels of FA have steeply risen causing a dramatic shift in the folate status of pregnant Canadian women; raising concerns over higher than recommended FA intake and the misalignment between current expert guidelines and the FA-content of PVS (50,99). Pregnancy is a critical period of plasticity whereby environmental factors, such as maternal nutrients, may impact fetal development and exert long-lasting effects on the offspring's growth and health into adulthood. This concept of fetal programming is well established in the literature (100–102).

1.3 Fetal programming and Epigenetics

It is beyond dispute that the incidence of neural tube defects has diminished considerably since the implementation of food fortification with folic acid, as well supplementation to the diet of women with a FA-containing multivitamins (40,42,103,104). Despite the success of these ongoing public health initiatives, the safety of high FA intake, particularly during pregnancy, has been the subject of intensive investigation. Evidence concerning long-term effects and disease susceptibility due to intrauterine exposure to environmental factors is growing. It is believed that epigenetic mechanisms, particularly DNA methylation, play an underlying role in early life origins of disease (85,105). Some of the health outcomes

being studied include metabolic syndrome, insulin resistance, respiratory illness (asthma and wheezing), allergies and skin sensitivities (eczema and atopic dermatitis) and adverse birth outcomes such as small for gestation height and weight as described later in section 1.4 (106).

The intrauterine environment is critical for fetal growth and development and therefore maternal environmental insults during this time such as poor nutrition, severe stress or illness may induce fetal responses that permanently alter offspring phenotype at birth (101,107). Nutrition is a major environmental factor that plays a role in fetal programming and is capable of inducing in utero modifications that can ultimately lead to permanent changes in metabolism and susceptibility to adult diseases (108,109). Periconceptional nutrition has been shown to affect fetal and postnatal developmental trajectories through epigenetic modifications of the genome by altering DNA methylation patterns, histone modifications and non-coding RNAs (108,110). Epigenetic changes are not mediated by DNA sequence alterations and they can result in long lasting effects on health by affecting gene expression. Establishing proper methylation patterns during early embryogenesis and fetal development is of utmost importance and is facilitated by nutrients that function as methyl donors and cofactors such as folic acid (111,112). The epigenome encompasses all chemical alterations of a cell involved in regulating gene expression (113). Improper establishment of the fetal epigenome can result from suboptimal nutrient availability prenatally and throughout gestation, impacting both short and long-term gene expression patterns in the offspring and is suggested to be implicated in the establishment of adult onset diseases (114–117).

Wolff et al. conducted the first study to find a clear mechanism for the effect of maternal nutrition on disease development in mammals without mutating the offspring's genes. The study demonstrated that outside factors, such as vitamin intake during pregnancy, can have a direct impact on the metabolism, development and gene expression of offspring (118). Pregnant black agouti mice were fed methyl-supplemented diets, which led to altered epigenetic regulation of agouti expression in their offspring, as

indicated by increased agouti/black mottling in the direction of the pseudoagouti phenotype (118). This study revealed that high intakes of methyl donors during pregnancy, such as folate, are able to have direct implications on the coat colour and disease susceptibility of newborn mice.

As mentioned earlier, folate is a key micronutrient required for the rapid proliferation of cells, the development of the uterus and placenta, and to support increased maternal blood volume during pregnancy (62). The proposal that nutrition in fetal life is a central stimulus for programming and susceptibility of adult disease in humans is supported by the Dutch Hunger Winter studies (119,120). During the winter of 1944 to 1945, the western part of the Netherlands was struck by a period of severe food scarcity. Nutrition prior to the war was adequate, however, by April 1945 rations were as low as 500 kcal per day (121). Food supplies were restored immediately after liberation on May 5, 1945. Thanks to this historical data, it is possible to accurately define the beginning and the end of the famine period, which has led to extensive examination of its repercussions. The famine affected fertility, weight gain during pregnancy and maternal blood pressure (121). Studies also showed that women exposed during pregnancy to nutritional deprivation, imposed by severe famine, had offspring with reduced birth size (122) and an increased risk of glucose intolerance (123) and obesity in adult life (124,125). An ongoing study of the children of the Dutch Hunger Winter show that in addition to the aforementioned effects of food restriction in utero on metabolism and cardiovascular health, there are effects on age-associated decline of cognitive functions (126). Furthermore, after the liberation and restoration of food supplies, birth weights and other measures of infant size rapidly rebounded to pre-famine levels (127), leaving the offspring of this historical period of time with long-term consequences. Furthermore, there is also evidence of intergenerational and transgenerational effects of prenatal exposure to the 1944-45 Dutch famine (122,128,129). These studies confirmed generation-spanning effects of poor nutritional conditions during gestation such as increased adiposity, impaired glucose tolerance and altered cardiovascular function in the first and second generations (130), highlighting the importance of timing in prenatal

nutrition (131). This is especially true for a nutrient like FA that plays such a critical role in a range of biological processes implicated in fetal development and health.

1.3.1 DNA methylation

As previously mentioned, studies have demonstrated that maternal exposure to certain environmental and dietary factors during early embryonic development can influence the phenotype of offspring, as well as the risk of disease development later in life. Methylation of DNA is one of several epigenetic mechanisms that play a regulatory role in genome programming and imprinting during embryogenesis. Similarly, elevated homocysteine levels have been associated with fetal growth restriction and shorter gestation, emphasizing the influence of the one-carbon metabolism cycle on fetal growth and development. Furthermore, alterations in methylation patterns due to suboptimal folate intake may adversely affect epigenetic regulation of gene expression and influence pregnancy outcomes (18,132,133).

The epigenetic phenomenon known as DNA methylation is central to compromised embryonic development caused by disruptions in genes that encode enzymes in the folate metabolic pathway such as methylenetetrahydrofolate reductase (MTHFR) (134). DNA methylation is catalyzed by methyltransferases that use the universal methyl donor, SAM, to modulate gene expression and genomic integrity (135). MTHFR is responsible for synthesizing 5-MTHF, the primary form of circulating folate and the methyl donor for synthesis of methionine from homocysteine and precursor of SAM. Polymorphisms in MTHFR lead to an increased risk for NTDs and other adverse embryonic outcomes (134,136).

Dietary methyl donors have a crucial impact on DNA methylation, which is the addition of a methyl group to the cytosine residue present in cytosine-guanosine (CpG) dinucleotides (117). CpG dinucleotides occur at low abundance and tend to concentrate in regions known as CpG islands which are found in the promoter regions of roughly half of the genes in the human DNA genome, namely the housekeeping genes

(117,137). CpG dinucleotides are primarily methylated in non-promotor regions and unmethylated in promoter regions (137,138). Methylation within the promoter region correlates with transcriptional silencing by inducing chromatin condensation (139) and the methylation status of CpG islands is believed to regulate gene transcription through the inhibition of transcription factor binding either directly or via altered histone acetylation (138). Most human transcription factors have CG-rich binding sites, therefore, methylation of these regions can inhibit the transcription factors' abilities to access the DNA, leading to suppression of gene expression (139).

During early gestation, DNA methylation patterns are undergoing critical development and maturation. Permanent changes to CpG methylation can result from a nutritional status affecting the transfer of methyl groups (140). Consequently, alterations in folate-dependent one-carbon metabolism during pregnancy can significantly affect DNA methylation in the offspring, having long-term health consequences (141). Additionally, it has been shown that nutritional supplementation during pregnancy can increase methylation of specific genes, and therefore, permanently alter gene expression (142). Aberrant DNA methylation has been implicated in the pathogenesis of a number of diseases associated with aging, including cancer and cardiovascular and neurological diseases. Evidence is accumulating that dietary factors, in utero, modulate disease risk (141–143). It is becoming apparent that epigenetic changes constitute a major link between early environmental exposure, including nutrition, and disease development later in life (144).

1.4 Adverse effects of high folic acid intake

With mounting awareness regarding the use of folic acid supplementation to improve birth outcomes, concerns have been raised about high folate status, with the greatest observed increase being in pregnant women (145,146). These studies reported that the highest folate status were found among pregnant women, as a result of FA supplementation in addition to FA fortification (145,146). Studies

observing thousands of pregnant Canadian women's intake of FA have found that the proportion of supplement-consuming women exceeding the UL is between 85-90% (79–82). Moreover, despite the proposed UL, there is no consensus on a safe upper limit of blood folate (61,147,148). The adverse effects of high FA levels during pregnancy, including short-term and long-term effects on fetal metabolism and development, have only been explored in a limited number of studies and findings vary.

1.4.1 Maternal outcomes

Exposure to high intake of folic acid during pregnancy means that both the mother and fetus are exposed to FA at higher than recommended levels. Safety concerns were first raised based on early reports of adverse health outcome in elderly with low vitamin B12 status who took high doses of FA; explaining the entwined history between high FA intake and pernicious anemia, a disease caused by vitamin B12 deficiency (99). Therefore, the risks of high FA intake in the presence of unrecognized vitamin B12 deficiency have been widely accepted (149–153). The direct maternal implications as a result of high FA intake during pregnancy are less clear, however. Described in section 1.1.1, before having any coenzymatic activity, FA must be reduced and converted to THF and then 5-MTHF. The limitation of this metabolic process results in circulating unmetabolized folic acid, especially when overly saturated levels are being reached. Although there is no absolute consensus in the literature, several maternal outcomes have, and continue to be investigated, including gestational diabetes. Studies have found that high FA intake in early pregnancy increases the risk of gestational diabetes mellitus (GDM) (154–156). Lai et al. investigated blood samples of 913 mother-offspring pairs in Singapore to assess plasma concentrations of folate during gestation and the association with GDM (154). An odds ratio of 1.97 of GDM was observed in women with combined vitamin B12 insufficiency and highest concentrations of folate; however, no significant associations between increasing folate concentrations and GDM were found among women with normal vitamin B12 status (154). Similarly, Zhu et al. used data from a Chinese prospective cohort study (n=3474) to explore the association between FA supplement consumption during pregnancy and

risk of GDM (155). GDM was diagnosed in 13% of women and it was found that increased risk of GDM was associated to daily supplement consumption in the first trimester (adjusted odds ratio of 2.25, 95% confidence interval 1.35-3.76) (155). Comparable to North American findings, less than 1% of the abovementioned cohorts were folate deficient. The underlying mechanism of this adverse effect is unclear; however, Zhu et al. support that there are at least the following two possible explanations. The first may be an imbalance between vitamin B12 and folate. A high folate status could exaggerate the metabolic effects of vitamin B12 deficiency and might participate in the pathogenesis of GDM through worsening insulin resistance (157). The second possible explanation appraised by Zhu et al. are the potential harmful effects of unmetabolized plasma FA. It has been reported to be related to decreased natural killer cell cytoactivity (158), which has also been suggested to be involved in the pathogenesis of GDM (159). Preedy et al. state that folate may be involved in the pathogenesis of glucose intolerance due to the inability to regulate the synthesis of homocysteine (156). Elevated concentrations of homocysteine have been linked to insulin resistance and associated metabolic abnormalities (160,161). Although we regard the intrauterine environment during the periconceptional period as highly sensitive, high FA intake is also capable of resulting in adverse maternal health consequences, regardless of the mode of action. These findings remind us why it is essential that a comprehensive investigation into the safe therapeutic window is also undertaken.

1.4.2 Birth/Child Outcomes

That being said, high micronutrient intake and exposure may impact the fetus in a more severe and long lasting manner. There is a growing concern over the effect of high FA intake during pregnancy on birth outcomes. A pregnant cohort of women in Spain examined periconceptional use of FA supplements and small for gestational age weight and height (n=786) (162). Babies born to mothers who consumed high doses of FA supplements (>1mg/d, ranging from 2.5 to 10.5mg/d) had a significant reduction in mean birth height compared with babies of non-users (162). In regard to weight, mothers

using high doses of FA supplements had lower-birth-weight babies for gestational age than non-users. These findings suggest that periconceptional use of FA supplements greater than 1 mg/d is associated with decreased birth height and may entail a risk of decreased birth weight (162). Further, Yajnik et al. studied the association between maternal total homocysteine and offspring birthweight in the Pune Maternal Nutrition Study (n=526) and Parthenon Cohort Study (n=515), both of which took place in India (132). The study tested for evidence of causality between disturbed one-carbon metabolism due to high homocysteine concentrations and poor fetal growth, using neonatal birthweight as a measure. Evidence of causality was tested within a Mendelian randomization framework, using a MTHFR gene variant, rs1801133, by instrumental variable and triangulation analysis, separately and using meta-analysis. Findings from this study confirm the association between maternal one-carbon metabolism and fetal growth, and that reducing maternal homocysteine concentrations may improve fetal health outcomes (132). It is increasingly apparent that due to FA's involved role in fetal programming, prenatal exposure to FA should not be taken lightly. Despite a lack of reliable conclusions regarding cause and effect, emphasis on the importance of following evidence-based recommendations remains equally relevant as childhood outcomes continue to support the need for further investigations.

The Norwegian Mother and Child Cohort Study (n=32,077) investigated the relationship between folate supplements in pregnancy and early childhood respiratory health. This study concluded that taking FA supplements, containing ≥400 μg of FA during both the first and second trimesters, was associated with a greater prevalence of respiratory illness and wheeze (163). Similarly, the association between folate and asthma was examined by Whitrow et al. using an Australian birth cohort (n=557). The study's primary outcome was physician-diagnosed asthma, which was reported in 11.6% of children at 3.5 years and in 11.8% of children at 5.5 years (164). In this study, folic acid taken in supplement form in late pregnancy was associated with an increased risk of childhood asthma at 3.5 years and with persistent asthma, which was affirmed if the child had asthma at both 3.5 years and 5.5 years (164). The amount of maternal FA

consumed during early and late pregnancy varied; however, the study reported that standalone supplements contained a higher dose of FA than did multivitamins. Consequently, in early pregnancy, the median intake of FA from standalone supplements was 2,948 µg/day compared with 500 µg/day in a multivitamin (164). Also explored, has been the relationship between maternal folate status in pregnancy and allergic outcomes in early childhood. Dunstan et al. examined infant allergic outcomes at one year of age (n=484) (165). The amount of FA taken per day as a supplement was categorized into tertiles <200 µg, 200-500 µg and >500 µg of FA/d. Eczema was the only associated allergic outcome; however, subsequent eczema was significantly associated to mother's who had consumed supplements in higher doses during the third trimester (165). Similarly, a population-based birth cohort study in the Netherlands (n=8742) found that highest maternal plasma folate concentrations during the first trimester were positively associated with the development and increased prevalence of atopic dermatitis in offspring (166). Additionally, Magdelijns et al. showed an increased risk of eczema in the offspring of mothers using FA supplements for the entire pregnancy; however, this association remained non-significant after adjustment of confounders (167). There remains a limited number of studies investigating the relationship between FA supplementation during pregnancy and childhood airway disease. In addition to the current studies lacking a level of evidential caliber, there are also a number of studies that found no evidence of an association between impaired folate metabolism and the development of atopy in children or adults (168,169).

Finally, adiposity and impaired insulin resistance are topics being explored in relation to high intakes of FA during pregnancy. Small size at birth is a risk factor for type 2 diabetes mellitus, while raised maternal plasma total homocysteine concentrations predict small birth size (22,170). This led Yajnik et al. to also use the data collected in the Pune Maternal Nutrition Study in India to examine the association between maternal folate and homocysteine status during pregnancy and offspring adiposity and insulin resistance at six years old (n=674) (171). Although the children appeared short and thin, they were

relatively adipose, meaning they possessed higher body fat percent, central fat and skinfold thickness in comparison to UK standards. Higher maternal blood folate concentrations at 28 weeks predicted higher offspring adiposity and higher insulin resistance (171).

The burden of chronic non-communicable diseases such as diabetes and obesity is shifting rapidly. It warrants a review of the classic dogma of genetic predisposition, precipitated by adult lifestyle. The paradigm of early life origins of chronic disease has focused attention on maternal health and nutrition as major determinants of the health of the offspring (170). In conclusion, the current state of evidence remains inconclusive and the risk of high folic acid intake during pregnancy is not entirely certain. The available literature contributing to the current state of evidence heavily relies on observational, cross-sectional, cohort studies that have revealed certain associations described above; however, there is a lack of strong hierarchically ranked RCTs and subsequent systematic reviews and meta-analyses to draw definitive conclusions. Nonetheless, it is certain that folate is a crucial nutrient during pregnancy, and its fortification in several countries has proven to be a remarkable implementation for the prevention of folate-dependent NTDs. However, presently, NTDs are uncommon in Canada and 40% of Canadians have high folate status (70). Accordingly, concerns over the effects of high folate consumption as well as other dietary methyl donor intakes are beginning to rise.

1.5 Preconception care (PCC) & Primary Care Physicians

It is undeniable that folate is essential to ensure optimal pregnancy outcomes, however, the long-term consequences of high blood folate concentrations on fetal development due to epigenetic programming or other mechanisms are not yet clear. Given that there is no additional benefit of higher than recommended doses of FA and the findings from current literature, the precautionary principle can be applied in clinical practice to anticipate unintended adverse consequences that may arise (172,173). Preconception care (PCC) is defined as the promotion of the health and well-being of a women and her

partner before pregnancy in order to identify medical and psychosocial conditions that may put the mother or fetus at risk (174,175). Ensuring that PCC is delivered ahead of time is central since the traditional early prenatal visit is too late to affect reproductive outcomes. The concepts of preconception care have been articulated for over a decade; unfortunately, it has yet to become a part of routine practice (176). Many studies have examined the effectiveness of interventions targeted to increase awareness of preconception FA supplementation (177–184); however, less is known regarding the link between preconception health promotion and improved pregnancy outcomes. Preconception care could reduce the prevalence of congenital anomalies because it occurs before the critical period of organogenesis (day 17 to 56 after conception) unlike prenatal counselling (185).

Since PCC is a set of interventions that aim to identify and modify risks to a woman's health or pregnancy outcome through prevention and management, it should occur any time a health care provider sees a WCBA. Personal and family history, reproductive planning, nutrition, supplements, weight, exercise, vaccinations, and injury prevention should be reviewed with all women. It is an opportune time to ensure that women are aware of the daily folic acid recommendation of 400 µg, as well as encouragement of proper diet and exercise (186).

Frey and Files surveyed 499 American women aged 18 to 45 years about pregnancy planning, knowledge and attitudes about PCC, and personal preferences for sources of health information regarding PCC. They found that although nearly all women (98.6%) realized the importance of optimizing their health prior to a pregnancy, only 39% could ever recall their physician discussing preconception health with them (176). Of the women who had previously been pregnant, only 47.2% of instances were planned. This is consistent with Canadian trends that state half of pregnancies are unplanned, which is concerning because 23% of women aged 20-34 smoke and 73% of women consume alcohol (187). The Government of Canada recommends health care providers to recommend a daily multivitamin containing 400 µg of FA for all WCBA who could become pregnant, and to discuss risk factors that may warrant a higher dose

(187). When asked about their preferences of sources to receive preconception health information, a majority of the study's women said that they preferred their physician.

PCC and primary care physicians are central to ensuring the health status of parents prior to conception and subsequently, they are critical in reducing individual and environmental factors that could contribute to poor maternal and child health outcomes. The SOGC guidelines recommend that all women in the reproductive age group (12-45 years of age) who have preserved fertility (a pregnancy is possible) should be advised about the benefits of FA in a multivitamin supplementation during medical wellness visits (e.g., birth control renewal, Pap testing and yearly examination) whether or not a pregnancy is contemplated (5).

Physicians are the linking bodies between expert guidelines and women and thus, it is imperative that they keep up to date to best inform their patients. Physicians have a unique positionality and are a key stakeholder group in ensuring the health of women, their babies, and being capable to influence the pharmaceutical industry. Although physicians' recommendations are highly influential to an expecting mother, as previously described, there currently does not exist a widely available PVS containing 400 μg of FA. Consequently, the misalignment inhibits physicians and women from following the SOGC guidelines and public health recommendations.

Chapter 2: Hypotheses and Objectives

2.1 Study Rationale

Since the association between folic acid deficiency and spina bifida was first published in 1965 (43), it has been conclusively shown that maternal FA supplementation during the periconceptional period can drastically reduce the risk of spina bifida and other neural tube defects in low, moderate and high risk pregnancies (47,48,103). The results of these studies, and others alike, have confirmed the detrimental effects of various maternal nutrient deficiencies, including folic acid, on fetal development and pregnancy outcomes (188). The significance of those findings led to the development and recommended use of multivitamin supplements to help promote healthy pregnancy. Health Canada and the SOGC recommend low-risk women to consume a daily oral multivitamin supplement containing 400 µg of folic acid prior to conception, throughout pregnancy and as long as breastfeeding continues, regardless of their nutritional status, to ensure adequate vitamin and mineral levels throughout gestation (5).

During the course of gestation, there are a remarkable series of maternal physiological and metabolic adjustments aimed to support the growth and development of the fetus and placenta; undoubtedly, affecting the need and utilization of nutrients (189). The use of prenatal multivitamin supplements has been shown to lead to excessive FA intake levels, due to the high supplemental dose found in prenatal vitamin supplements coupled with FA-fortified staple foods. The literature confirms that high intake of vitamins, specifically FA, is a reality for many WCBA and a majority of pregnant women due to healthcare professionals recommending intake of PVS and those that are available containing too much FA. This highlights the impact that the misalignment between expert guidelines and the FA-content in prenatal vitamin supplements has on the suboptimal intake of FA by women in Canada, as well as North America. Amounting evidence that high folic acid intake can induce adverse effects in both animal and human models and may have a severe impact on fetal health and development, have been observed.

Nevertheless, limited studies have directly focused on the misalignment between guideline recommendations and the high supplemental content of FA causing this reality for majority of supplement consumers. Recognizing the misalignment and furthermore, how to mitigate it, is warrant. Limited studies have focused on, and targeted, physicians; regardless of the fact that they are women's preferred source for preconception information and the linking body between guidelines and consumers. Physicians are a critical linking piece in breaking the cycle and moving forward with a supplement that is in line with recommendations; however, currently, very little is known about physicians' knowledge regarding high FA intake, the SOGC guidelines generally, and their stance on the misalignment. Thus, this study was designed to assess physicians' current knowledge and attitude about the SOGC guidelines, folic acid intake and its health-related outcomes and how it influences both their current and future practices. Physicians' knowledge and attitude, especially their willingness to recommend a supplement containing 400 µg of FA, could be the missing piece of evidence to influence pharmaceutical companies to produce a widely available prenatal vitamin supplement containing 400 µg-FA and to enable a sustainable change to align FA intake during the periconceptional period with evidence-based recommendations.

2.2 Hypothesis

The overarching hypothesis of the current research study is that the extent of physicians' knowledge of SOGC guidelines and FA-related topics will positively influence their willingness to prescribe a multivitamin supplement containing 400 µg of folic acid.

2.3 Specific Objectives

Specific Quantitative Research Objectives

1) To assess physicians' knowledge regarding FA including perinatal recommendations, Canadian pregnant women's status, and health-related outcomes.

2) To assess physicians' current practice regarding FA.

3) To assess physicians' attitude toward current practice and perinatal recommendations.

Specific Qualitative Research Question

1) What are the physician's perceptions and barriers regarding the misalignment between FA supplement content and recommendations?

Chapter 3: Methods

3.1 Study Design

This is a cross-sectional study consisting of a mixed method research design. The nature of the objectives and data to be collected presented itself as strong rationale for a mixed methods research approach (190). Knowledge, attitude, and practice (KAP) studies can guide the implementation of public health interventions and they are important tools for persuasion and thus, such a research tool was selected (191).

3.2 Population

This study recruited physicians practicing in family health teams (FHTs), family health organizations (FHO), private practices and hospitals in the National Capital Region of Canada between August 2018 and May 2019. Physicians who were willing to participate and complete the questionnaire were included for the study. Any physician who did not speak one of the two official languages (English or French) would have been excluded, although this did not happened. Although general practitioners were targeted, obstetrician-gynecologists (OBGYN), surgeons, medical residents, and medical students were eligible to participate. Of the 111 FHT and clinics that were approached and invited to participate in the study, 15 agreed to scheduling a visit to the site. Visits to The Ottawa Hospital (TOH) and Hôpital Montfort's Grand Rounds were coordinated through hospital affiliate, and thesis advisory committee member, Dr. Vincent della Zazzera.

3.3 Sample Size Calculation

The sample size was based on a study conducted by Askarian et al. that measured the levels of knowledge, attitudes, and practice toward standard precautions among physicians and surgeons in university-affiliated hospitals of Shiraz, Iran (192). Due to available resources and feasibility of this pilot study, a target sample size of 88 physicians was determined to detect a correlation coefficient between

knowledge and attitude and/or practice of at least 0.29 with a significance level, or alpha (α) of 0.05 (2-sided test) and a power set to 80%.

3.4 Participant Recruitment

Initially, a list of all FHTs and clinics within a feasible distance (30 kilometres) from the University of Ottawa main campus was generated and selected through both a convenience and random methods. The number of physicians attending hospital Grand Rounds or practicing at any given FHT/clinic is highly variable. The initial sample size was determined to be 88, however, collection of data ceased with 77 physicians due to time constraints and feasibility. Included were all family physicians practicing in FHTs, FHOs and private practices within the determined radius. The initial sample frame (list of family physicians) was obtained from the online CFPC member list directory. Search limits included the province of Ontario and the city of Ottawa. The search yielded 1200 physicians with special designations such as EM (emergence medicine), PC (palliative care), or SEM (sports and exercise). In efforts to assess physicians with a higher probability of seeing WCBA/WCBA-patients and pregnant women, approximately 150 Ottawa physicians who hold these special designations were excluded from the total population sample number, yielding a total target population of 1050 physicians.

3.4.1 Calling FHT visits

The initial list of randomly selected FHTs was entered into REDCap, which also housed the recruitment script and allowed for recruitment management (see Appendix A). FHTs and clinics were contacted by phone and/or electronically. Once a point of communication was established, the project was explained to the clinic manager or coordinator to obtain approval to further recruit willing physicians. If accepted, an invitation poster was sent by email or fax in either official language (see Appendix B). Follow-up calls and emails were made until a final decision was made by the medical centre. If they

accepted to participate, an in-person visit was scheduled to distribute the questionnaires and if not, the clinic was kindly thanked.

After multiple months of recruitment with a very low success rate, convenience and snowball sampling techniques were adapted and the list of clinic records grew from 66 to a total of 111 by the end of recruitment. The additional FHTs/clinics were found by searching the Hôpital Montfort's website physician directory and filtering by specialty. The criteria applied was "Family Medicine" (54 results) and "Family physician doing obstetrics" (14 results). The address and telephone number of their main place of practice was publicly available and used to expand the list of clinics to recruit. The clinics that were contacted were categorized as 'FHT', 'hospital' and 'clinic'. 44.2% (34/77), 32.5% (25/77) and 23.4% (18/77) participants were recruited from FHTs, hospitals and clinics, respectively.

3.4.2 Scheduling Hospital Grand Rounds

Both The Ottawa Hospital and Hôpital Montfort hold weekly medical Grand Rounds (GR) for different departments and divisions. At TOH, GRs are hosted by the Department of Medicine through the support of it's Continuing Medical Education Committee. Both hospitals requested institutional ethics approval in order to attend and present at their Department of Obstetrics and Gynaecology Grand Rounds. An educational seminar presentation entitled "Current State of Evidence for Perinatal Folic Acid: Recommendations, Intake and the Status of Canadian Women" was delivered at Hôpital Montfort's GR on November 21, 2018 and at TOH's GR on January 9, 2019.

Medical regulatory bodies such as the The College of Family Physicians Canada (CFPC) and The College of Physicians and Surgeons of Ontario (CPSO) encourage family physicians to keep current with medical and health care developments by participating in activity sessions that constitute continuing professional development (CPD). As an incentive to participate and to contribute toward education, a

brief, 20-minute informative/educational seminar was created and delivered to participants in a similar style of a CPD program, however, no credits were earned toward physicians' annual CPD goal.

3.5 Data Collection

Physicians are notoriously known to yield poor response rates (193,194). In order to address this challenge, participants had to complete a hard copy of the questionnaire in person during the time of the visit. In all cases, whether recruited from FHTs, hospitals or clinics, the physicians completed and returned the questionnaire prior to the educational/incentive portion. This procedure was followed in order to both maximize participation and avoid influencing their responses.

It was clear right away that a lack of time was an issue for most clinics and thus, the seminar was presented only a few times before an educational package version of the material was formed. The visit time was reduced significantly to approximately 15 minutes total and the PDF package was sent to physicians afterward. During both Grand Round visits at the hospitals, the attendees were first asked to complete the questionnaire. Once every questionnaire was returned, the educational seminar was delivered, followed by a questions/discussion period.

3.5.1 Questionnaire Design and Content

Questionnaires from previous KAP studies were used as guidelines and adapted to the context of this study. On November 17, 2017, thirty-eight participants from across the country and some from the United States, attended a one-day workshop that was held in Ottawa, representing key stakeholder groups including academia, industry, government and healthcare professional associations. The workshop aimed to convene key stakeholders to address the misalignment between expert guidelines and FA supplement content (50). Five challenges in aligning perinatal FA intake with expert guidelines emerged from the workshop as well as their potentially associated solutions. The five themes that emerged from the workshop's discussions were 1) the need for additional evidence on the effective dose and duration

to prevent neural tube defects; 2) the need for supplement content that is consistent with recommendations; 3) facilitating access to folic acid-containing supplement around preconception, particularly for vulnerable women; 4) knowledge transfer because of low awareness of recommendations; and 5) change the "*more is better*" attitude when it comes multivitamin supplements (50). The questionnaire was developed as a knowledge, attitude, and practice assessment tool with regard to physicians' supplemental folic acid recommendations during the periconceptional period. The questionnaire's first section was designed to capture participants' general characteristics followed by the knowledge section, which covered general FA-related health topics as well as low, moderate and high-risk recommendations as outlined in the 2015 SOGC clinical practice guideline. The attitude and practice sections followed. These sections were designed to capture physicians' familiarity, and attitude toward the most recent SOGC guidelines and to understand both their current and future practice in relation to the guideline recommendations. Finally, a statement from the SOGC guideline was presented and the subsequent questions allowed participants to reflect on their attitude and practice given the current and accurate recommendation followed by the opportunity to express how they perceive the misalignment and if they encounter any barriers or challenges in adhering to the guidelines. The instrument consisted of 32 items, including 20 multiple-choice questions, 8 Likert-scale or yes/no answers and 4 open-ended questions. Under all circumstances, the surveys were answered anonymously. Personal characteristics such as sex, age, and number of years of practice were collected; however, a four-digit participant ID was randomly generated and assigned to each participant's questionnaire. To acknowledge the limited amount of time physicians have to participate, the questionnaire was designed to be completed in a maximum total time of ten minutes.

3.5.2 Translation and Validation

Questionnaires were validated through consultations with a committee of non-participating physicians and experts to eliminate ambiguity and biases (195–197). The distributed questionnaire was available in both English and French to accommodate the bilingualism of the National Capital Region. The questionnaire was initially developed in English and then translated to French following the linguistic validation methodology described by Vallerand (198). The original questionnaire was translated from English (source language) into French (target language) as follows: 1) original instrument was translated into French by a bilingual individual; 2) a second bilingual individual then translated the instrument back into English, without access to the original instrument. These steps were repeated with another pair of bilingual individuals; 3) the two back-translated instruments were compared against the original instrument to determine optimal terms to be used (198). To ensure clarity and minimize ambiguity of the questionnaire, bilingual physicians/OBGYNs and researchers with an expertise in mixed methods research were consulted.

3.6 Data Analyses

All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 to assess physicians' level of knowledge regarding FA including perinatal recommendations, Canadian pregnant women's status, and health-related outcomes as well as their attitude toward current practice and perinatal recommendations. Initially, exploratory and descriptive statistics were conducted to examine data (e.g. mean and frequency distributions; outliers). The total knowledge, attitude and practice scores (TKS, TAS and TPS, respectively) were calculated as well as the two sub knowledge scores, KS1 and KS2, by summing up the allotted weight of correctly answered questions relating to low, moderate and high risk FA recommendations during pregnancy and FA health-related topics. The sub and total KAP scores were normally distributed. General linear models were used to assess different knowledge,

attitude and practice scores between study sample characteristics (e.g., age, years of practice, type of practice, place of employment and number of pregnant and WCBA seen per week) and Tukey's post hoc tests were performed to compare and examine differences among the subgroups. Pearson correlation tests were performed to find association between all sub and total KAP scores. Pearson's correlations were used since the KAP scores were continuous and normally distributed. By convention, the level of statistical significance was set at less than 0.05.

3.7 Ethics

This research study obtained ethics approval from the research ethics boards (REB) of the University of Ottawa (Appendix A), The Ottawa Hospital (Appendix B), and Hôpital Montfort (Appendix C). Informed consent was obtained from all participants prior to participation, which also complied in accordance to the established conditions. All ethical requirements outlined by the REBs with regard to individual privacy, data confidentially and conservation of data have been respected.

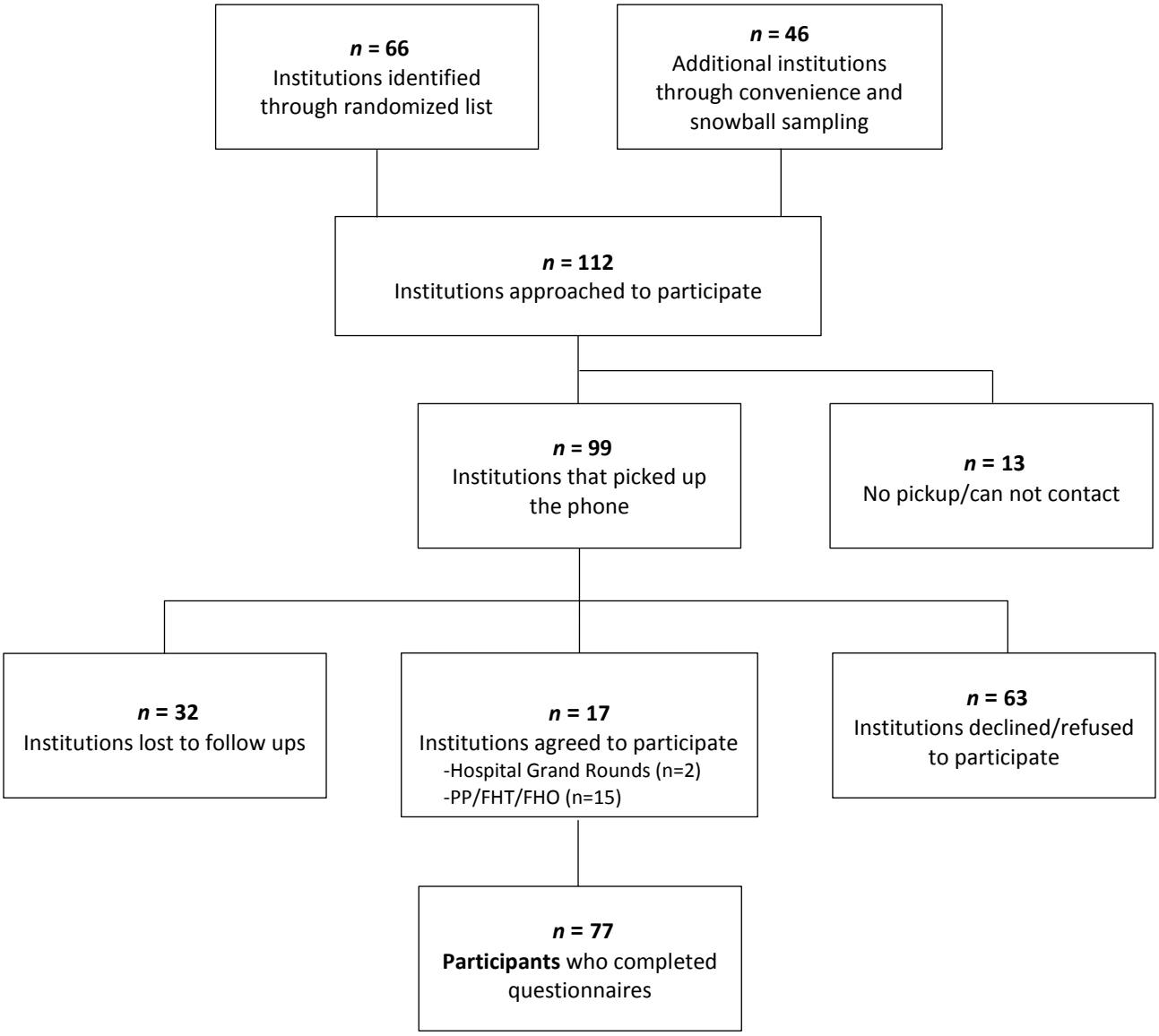

Figure 3. Recruitment flowchart Representation of recruitment of study participants (n=77).

Chapter 4:

Knowledge, Attitude and Practice of Physicians Regarding Periconceptional Folic Acid

Liana Arielle Mida[a], Vincent della Zazzera[b], and Bénédicte Fontaine-Bisson[c,d]
[a] Interdisciplinary School of Health Sciences, University of Ottawa, 25 University Private, Ottawa, Canada;
[b] The Ottawa Hospital, 501 Smyth Road, Ottawa, Canada;
[c] School of Nutrition Sciences, University of Ottawa, 25 University Private, K1N 6N5, Ottawa, Canada;
[d] Institut du savoir Montfort, Hôpital Montfort, 713 Montreal Road, Ottawa, Canada; (Corresponding author)

4.1 Abstract

Background. Canadian expert guidelines recommend low-risk women to consume a daily multivitamin supplement containing 400 µg of folic acid (FA) to prevent neural tube defects. Mandatory food fortification coupled with intake of prenatal vitamin/mineral supplements (PVS), most of which contain ≥1000 µg-FA, has resulted in an unprecedented shift in Canadian pregnant women folate status. This study assessed the knowledge, attitude and practice (KAP) of physicians regarding periconceptional FA recommendations, intake and health related outcomes, since they play an essential role in promoting appropriate FA intake.

Methods. As part of this cross-sectional study, 77 physicians practicing in the National Capital Region answered a self-administered survey.

Results. Only half of physicians knew the correct dose and duration of FA for low-risk women and less than 30% had the correct answer for other knowledge-related statements. Approximately 70% were unsure of, or unfamiliar with the most recent guidelines and 60% of physicians most often recommend a ≥1000 µg-FA supplement. Knowledge score 1 (KS1), which related to low-risk women differed significantly between groups of physicians' attitude toward believing that most PVS contain the recommended amount of FA (p=0.004). Significant correlations were also found between KS1 and the total practice score (TPS) (r=0.45, p<0.0001) as well as between the total knowledge score and TPS (r=0.38, p=0.0007).

Conclusions. The study's findings show that physicians lack knowledge regarding periconceptional FA is associated with their attitude and practice. Despite a vast majority of physicians being unsure or uncomfortable recommending PVS that are not in line with recommendations, a lack of knowledge and a widely accessible 400 µg-FA PVS, enables a contradictory practice in reality. Educational programs targeted to physicians are needed to improve their KAP to ultimately ensure an appropriate intake of perinatal FA.

Keywords: Attitude; Folic Acid; Knowledge; Physicians; Practice; Pregnancy; Periconception; Guidelines

4.2 Introduction

Neural tube defects (NTDs), including spina bifida and anencephaly, result from failure of neural tube closure during the third and fourth weeks of gestation (1). They are among the most common, yet preventable, birth defects and an important health issue because of their detrimental physical, psychological and social impact on Canadian infants, children and their families (2,3). Worldwide, it is estimated that approximately 300,000 to 400,000 neonates are affected with NTDs each year, and 1 out of 2,500 births in Canada; thus, becoming a major cause of morbidity and mortality among fetuses and babies (4,5). Strong evidence from observational and randomized controlled trials has convincingly shown that folic acid (FA) can prevent the primary and secondary occurrence of NTDs (6–10). FA provides the universal methyl-group required for one-carbon transfer pathways, which are fundamental in amino acid metabolism, as well as DNA synthesis, repair and methylation, all of which are imperative during periods of fast cellular division and replication such as fetal development (11–14). Prevention of NTDs with optimal FA intake is thus a major public health concern.

Internationally, periconceptional supplementation with 400 µg of FA is recommended for the prevention of NTDs (4,15,16). Today, 82 countries, including Canada, have legislation to mandate nationwide mandatory fortification programs in which at least one industrially milled cereal grain product (e.g., wheat flour, maize, or rice) is fortified with folic acid (17,18) which has significantly decreased the prevalence of NTDs in those countries (1,19,20). The Government of Canada and the Society of Obstetricians and Gynaecologists of Canada (SOGC) both recommend a daily multivitamin supplement containing 400 µg of FA for the primary prevention of NTDs among low-risk women from before conception and throughout lactation (21). Despite these recommendations, a majority of prenatal supplements on the Canadian market contain an amount of FA that is equivalent to or exceeds the tolerable upper intake level (UL) of 1000 µg FA. Mandatory staple food fortification, coupled with high supplemental FA intake, has resulted in intake levels that exceed the UL and consequently high red blood

cell (RBC) folate concentrations among pregnant women and women of childbearing age (WCBA) across the country (22–27).

More recently, there is growing concern about this upward shit in FA intake and status in the pregnant population, due to it's role in epigenetic programming (11,13). Evidence from animal studies and some human epidemiologic data suggest that alterations in methylation patterns due to suboptimal FA intake can affect epigenetic regulation of gene expression with the capacity to adversely influence pregnancy outcomes (28–31). Though inconclusive, the associations between high FA intake and increased risk of respiratory disease, asthma, atopic dermatitis and bronchiolitis, in childhood of the offspring, have been raised (32,33). It is undeniable that folate is essential to ensure optimal pregnancy outcomes. The long-term consequences of high blood folate concentrations on fetal development due to epigenetic programming or other mechanisms are not yet clear, however.

Given that there is no documented additional benefit of higher than recommended doses of FA, the precautionary principle can be applied in clinical practice to anticipate unintended adverse consequences that may arise (34,35). Physicians play an important role in promoting FA intake; however, as women's preferred source for preconception information (36), it is imperative that physicians are kept up to date to best inform their patients. The misalignment between current Canadian expert guidelines and the FA-content in prenatal supplements prevents both physicians and women from adhering to clinical practice guidelines. Currently, very little is known about physicians' knowledge regarding periconceptional and perinatal FA-related issues and their stance on the misalignment between FA intake and SOGC recommendations. The present study assessed the knowledge, attitude and practice of physicians regarding periconceptional folic acid recommendations, intakes, and health-related outcomes.

4.3 Methods

Study design

A cross-sectional survey was administered to physicians from August 2018 to May 2019, in Canada's National Capital Region, i.e. the cities of Ottawa (Ontario) and Gatineau (Quebec).

Participants

A total number of 112 institutions (family health teams (FHTs), family health organizations (FHO), clinics and hospitals) were contacted by telephone to schedule in-person visits to distribute the self-administered anonymous questionnaires. Initially, random sampling targeted 66 institutions; however, due to recruitment challenges, an additional 46 institutions were identified and contacted through convenience and snowball sampling. To be included, physicians had to be practising at one of the aforementioned medical institutions and be fluent in one of the two official languages (English and/or French). Ethics approval was obtained from participating hospitals and the University of Ottawa. Medical Grand Rounds were used to facilitate recruitment at two local hospitals. In total, 77 physicians completed the survey.

Data collection

The questionnaire was available in English and French, consisting of both open and closed questions, including 20 multiple-choice questions, eight (8) Likert-scale or yes/no answers, and four (4) open-ended questions. A portion of the questionnaire's knowledge section, pertaining to FA recommendations and NTD-risk factors, was developed directly from the 2015 SOGC guideline (21). Sociodemographic and professional characteristics of the respondents such as sex, age, and number of years of practice were also collected. The knowledge, attitude and practice sections of the questionnaire were developed proceeding a 2017 workshop held in Ottawa that convened key stakeholders from academia, industry, government and health professional groups with the overall goal to identify challenges and solutions to aligning supplemental FA intakes with current evidence-based recommendations (33). The attitude and

practice sections were designed to capture physicians' familiarity, and attitude toward the most recent SOGC guidelines and to understand both their current and future practice in relation to the guideline recommendations. After being presented with the current and correct recommendation statement, three (3) open-ended questions (qualitative component) enabled physicians to express how they perceive the misalignment and if they encounter any barriers or challenges in adhering to the guidelines. The questionnaire was translated to French using the linguistic validation methodology described by Vallerand and validated through consultations with a committee of non-participating physicians and experts to eliminate ambiguity and biases (37).

Statistical analyses

All data was analyzed using Statistical Analysis Software (SAS version 9.4). Initially, exploratory statistics were performed to examine data distribution and potential errors in data entry. The survey's questions were categorized as knowledge, attitude or practice items (correct/incorrect answers) and summed up to obtain knowledge, attitude and practice scores. Eight questions worth one point each related to general knowledge of FA and low-risk recommendations, composing the first sub-knowledge score (KS1) and those relating to knowledge of moderate and high-risk factors for NTDs made up the second sub-knowledge score (KS2), where each risk factor was worth one point. The total knowledge score (TKS) encompasses the sum of the two sub-scores while items pertaining to physicians' attitude and practice accounted for the total attitude and practice scores, TAS and TPS, respectively. Six (6) 5-point Likert scale questions captured physicians' attitudes (strongly agree=5, agree=4, unsure=3, disagree=2 and strongly disagree=1); however, then merged and regrouped into agree, unsure or disagree attitude subgroups for comparison analyses. A total of four (4) questions assessed practice, where two (2) were multiple choice and two (2) were yes/no, carrying a potential weight of point each, alike. Descriptive statistics (i.e. means ± standard deviation (SD) or frequencies – n (%)) were used to describe the study's

sample characteristics and to summarize the total knowledge, attitude and practice scores (TKS, TAS and TPS, respectively) as well as the two sub-knowledge scores (KS1 and KS2).

General linear models were used to assess the sub and total knowledge scores against six attitude statements. Subsequently, Tukey's post hoc tests were conducted to compare differences among attitude subgroups, categorized as those who responded agree, unsure or disagree to the attitude statements. Similarly, general linear models were used to assess KAP against subgroups of sociodemographic and professional practice characteristics. Tukey's post hoc tests were performed to explore differences between mean total scores of KAP among sociodemographic and professional practice subgroups. Bonferroni correction for multiple hypothesis testing was also performed as appropriate to correct for multiple hypotheses testing issues. Since all scores were continuous and normally distributed, Pearson correlation tests were performed to examine the association between all sub and total KAP scores. Results were considered as significant when p-value <0.05.

4.4 Results

4.4.1 Study Population

A total of 17 institutions agreed to participate with a total of 77 questionnaires completed by physicians, irrespective of their specialty. The study sample consisted of a majority of females, family physicians, practicing in a hospital, or FHT or FHO setting as their primary place of employment **(Table 1)**. More than half of respondents were still in various stages of their professional training (e.g., medical students or residents). There was a similar distribution of physicians in all categories of years of practice, except for those having 16-25 years which represented approximately half of the other groups. A majority of the surveyed physicians saw ≤30 of both non-pregnant WCBA and pregnant women per week.

4.4.2 Knowledge, Attitude and Practice Scores

The sum of all correctly answered knowledge items was measured as a total knowledge score (TKS) that encompassed two sub-knowledge scores. The first sub-knowledge score (KS1) was a measure of

physician's level of general knowledge regarding FA and low-risk recommendations while the second sub-knowledge score (KS2) was a measure of physician's knowledge regarding moderate and high-risk factors for NTDs. In addition to identifying nine moderate or high-risk factors for NTDs, physicians' knowledge of the correct supplemental doses for women with moderate and high-NTD risk was assessed and contributed to KS2. With a possible maximum TKS score of 17, a majority of physicians answered more than half of the knowledge items incorrectly and no physician achieved a perfect score **(Table 2)**. With a potential total attitude score of 30, our results show that most physicians were unsure or had positive attitudes in regard to FA recommendations and health-related outcomes **(Table 2)**. In relation to the evidence-based clinical practice guidelines and the reality of physicians' practice, approximately half of physicians had good practice behaviours or answered the practice questions correctly; all sub and total KAP scores are presented as means±SD in **Table 2**.

4.4.2.1 Knowledge Statements

Approximately half of physicians knew the correct dose and duration of supplemental FA recommended by the SOGC (**Figure 1 – panel A**). Although half of physicians could identify the recommended 400-µg dose of FA for low-risk women from a multiple choice list, when physicians were asked to fill in the blank and provide the recommended dose for moderate risk women, only one respondent had the correct answer and no physician knew the recommendation for high-risk women. Only one physician knew the correct optimal blood folate concentration for NTD prevention while a few had knowledge on the current folate status of Canadian WCBA. Physicians were also asked to select among a set of potential personal or comorbid conditions which ones were not a risk factor, a moderate-risk factor or a high-risk factor for having a pregnancy affected by a NTD. Almost all physicians were aware that women with a previous NTD-affected pregnancy and most knew that women who have a personal NTD history, constitute high-risk factors **(Figure 1 – panel B)**. Knowledge of other risk factors from the

SOGC guideline, and distractor options, was much lower. Further, only one-third of physicians knew that women whose male partner with a NTD history is also a high-risk factor.

4.4.2.2 Attitude Statements

Attitudes toward current prenatal vitamin supplement recommendations were quite heterogeneous regarding the SOGC guidelines (**Table 3**). More than two-thirds of physicians were unsure or not familiar with the most recent SOGC guidelines. Although close to 90% of physicians agreed or were unsure whether most prenatal supplements contained the recommended dose of FA, almost all of them thought that their recommendations were in line with the most recent expert guidelines. Despite this misalignment, close to 85% of them were unsure or not comfortable recommending a prenatal vitamin supplement that was not in line with the guidelines. Overall, these finding put an emphasis on the misalignment and contradiction between physicians' attitude toward the recommendations and the reality of their professional practice.

4.4.2.3 Practice Statements

In terms of physicians' clinical practice, more than half believed that they followed the guidelines, which were believed to be in line with most available prenatal vitamin supplements. More than one-third simply did not know whether their practice was in line with recommendations and available PVS on the market, confirming the attitude findings. However, only one-third in fact recommend a supplement in line with the recommendations of 400 µg-FA, and more than half recommend a PVS containing ≥1 000µg-FA, again reflecting a lack of knowledge and awareness of the guidelines (**Table 4**). When asked about the reasoning behind the supplement they most often recommend, almost half of physicians responded that it was "for no particular reason" while a quarter of them indicated that their recommendations are due to it being women's preference (**Table 4**).

4.4.3 Associations between knowledge, attitude and practice

None of the attitude statements were significantly associated with any of the knowledge scores except for one **(Table 3)**. We found a significant relationship between the attitude score in regard to the fourth attitude statement ("most PVS contain the recommended amount of FA") and KS1 (p=0.004). Tukey's post hoc test revealed a statistically significant difference among subgroups for the association found between the fourth statement and KS1. The agree subgroup did not differ significantly from the unsure and disagree subgroups; however, the score from the unsure subgroup was significantly lower than that of the disagree subgroups **(Table 3)**. This result remained significant after Bonferroni correction for multiple comparisons (p=0.05/6 statements=0.008). Pearson correlations were also performed to assess the relationships between all sub and total scores (KS1, KS2, TKS, AS and PS). Both sub-knowledge scores were significantly associated with the total knowledge score (r=0.68, p<0.0001 for KS1 and TKS and r=0.72, p<0.0001 for KS2 and TKS). Pearson's correlation test also confirmed that KS1 and KS2 are not interrelated (r=-0.015, p=0.89) and thus, physicians' knowledge of low-risk recommendations does not necessarily seem to be associated with their knowledge of moderate and high risk recommendations and vice versa. Significant associations were also found between KS1 and TPS; r=0.45, p <0.0001, as well as between TKS and the TPS; r=0.38, p =0.0007. However, others were not significant correlations were observed the TKS, AS and PS (r=-0.09, p=0.39 for TKS and TAS and r=-0.13, p=0.26 for TAS and TPS). In summary, possessing more knowledge of FA-related topics and the guideline recommendations appears to be associated with improved practice.

4.4.4 Qualitative assessment of physicians' perceptions and barriers

The questionnaire's open-ended questions were an opportunity to capture physicians' perceptions and barriers regarding the misalignment between FA supplement content and recommendations. Approximately a quarter of respondents mentioned that they need to update themselves by reading the latest guidelines and intend to do so as a follow up to the survey. There were a number of physicians who pointed out the challenge that arises due to the discrepancy regarding supplemental doses of FA found in

prenatal vitamin supplements. It is a repercussion of the long-existing misalignment that inevitably presents as a barrier to adhering to the guidelines.

4.4.5 Associations between KAP scores and participant characteristics

Differences in total (and sub) scores of knowledge, attitude and practice and socio-demographic characteristics of participants are shown in **Table 5**. We found that older physicians had a significantly higher knowledge score regarding moderate and high-risk factors for NTDs (KS2). Physicians with 16-25 years of practice had a significantly higher KS2 (p=0.004) as well as TKS (p=0.002) compared with those with less or more years of practice. These two results remained significant after Bonferroni correction for multiple comparisons (threshold p=0.008). No other sociodemographic or professional practice-related characteristics were associated with any of the KAP scores.

4.5 Discussion

This study aimed to assess physicians' knowledge and attitude regarding the SOGC guidelines, FA intake and its health-related outcomes and furthermore, how that influences their practice. This study was designed to explore physicians' perceptions and barriers regarding the existing misalignment between FA supplement content and expert guidelines. Results obtained in the present study showed that physicians had some knowledge of FA, including periconceptional PVS recommendations and health related topics, however, the lack of some knowledge possibly led to the relatively low rate of correct practicing behaviours. Our findings suggest that the two main factors that were associated with the rate of correct knowledge were the age of physicians and the number of years of professional practice. Regardless of the current state of KAP scores, a vast majority of physicians are either unsure or would not feel comfortable recommending a prenatal vitamin supplement that is not in line with current guideline recommendations.

A majority of the literature, globally assesses the knowledge and awareness of FA in WCBA or pregnant women, but physicians are rarely the targeted population (38–44). Although some studies have addressed physicians' awareness and practicing behaviours regarding periconceptional folic acid, we are the first to do so in a Canadian context in addition to being the first study to have analyzed the link between physicians' KAP while addressing the currently existing misalignment between FA-content in PVS and expert guidelines. Most surveys reported in the literature reveal that physicians lack knowledge regarding folic acid recommendations during pregnancy (45–49). Aggarwal et al. assessed 48 pediatricians, 54 obstetricians and 100 recently qualified medical graduates in India regarding their awareness of FA dose, timing of supplementation and knowledge about its role in prevention of NTDs. In this study, it was observed that although a majority were aware that FA has a role in NTD prevention, knowledge about dose and timing of supplementation was lacking (45). Auriel et al. found that 88% of Israeli gynecologists, but only 60% of physicians always recommend FA prior to conception (46). In a similar study, Williams et al. also assessed US health care providers' knowledge and practice regarding FA for NTD prevention (47). Similarly to our findings, approximately half of the family physicians were knowledgeable about the correct low-risk dose, while dramatically fewer physicians knew the correct dose to prevent recurrence of a NTD (47). Regardless of their diverse geographic, economic and cultural/social settings, findings from the present study are in line with this literature, particularly concerning FA recommendations for moderate and high-risk women. Results from our study also support those reported in the literature indicating poor preconception practice behaviours, primarily due to a lack of knowledge or awareness, and the need for more educational resources to address this topic with physicians (50,51).

Physicians from the present study possessed some knowledge of folic acid; however, insufficient knowledge may have led to a lower rate of correct practicing behaviours. Despite half of physicians knowing the correct low-risk dose (400µg), in reality, a majority most often recommend a PVS containing

≥1 000µg-FA. These findings reflect physicians' perception of the current misalignment between the guidelines and FA-content in prenatal vitamin supplements. A majority of female patients seen by the physicians are inclusive to the WCBA range; thus, it was imperative to investigate the professional behaviours of the participating physicians regarding their PVS recommendations to low-risk patients. The two main factors that were associated with the rate of correct knowledge were found to be the age of physicians and the number of years of professional practice. Almost half of our sample was made up of physicians with less than five years of professional experience and thus, may be indicative of how beneficial it could be to update medical undergraduate and resident curricula to more formally address the current guidelines. Regardless of the current state of KAP scores, 85% of physicians were either unsure or uncomfortable recommending a prenatal vitamin supplement that is in disagreement with the guidelines, in contrast to their current practice.

Preconception care (PCC) is vital because, globally, women have poor knowledge of FA (38,42,52) and this is particularly true among women with a low socioeconomic status (39,41,53,54). This is especially concerning since approximately half of pregnancies in Canada are unplanned (55). The potential benefits of delivering PCC to WCBA were described by Reynolds in 1998, stating that if women were aware of their unhealthy lifestyles, they would change their behavior before, during and after their pregnancy, and the quality of life and general health of these women would rise (56). He also stated that there would be fewer unwanted pregnancies and pregnancy outcomes would improve by decreasing mortality and morbidity in both mother and child. This can be explained because PCC occurs before the critical period of organogenesis (day 17 to 56 after conception), in contrast to prenatal care, which is nowadays often the only care that is given, which occurs later in pregnancy. This has been concluded by several studies on the importance of providing PCC to all WCBA (57–61).

Perinatal counselling is an approach that requires an open dialogue between the physician and the woman, to allow a better understanding of the user's knowledge, perceptions and lifestyle (59). Similar

arguments have been made in support of PCC with regard to combined hormonal contraceptive methods (62). The Government of Canada and the SOGC alike, recommend health care providers to take advantage of episodic visits to identify health risks, offer related interventions and encourage positive health behaviours *prior* to conception (21,55). The two organizations also explicitly state that physicians should "*Recommend a daily multivitamin containing 400 mcg (0.4 mg) of folic acid for all women of reproductive age who could become pregnant, and discuss risk factors that may warrant a higher dose*" (21,55). Although women's understanding and prioritization of optimizing their health prior to conception varies, primary care physicians are women's continued preferred source for preconception information (36). Physicians' lack of knowledge is reflected in their poor prescribing practice of FA during the periconceptional period. Several studies, including the present one, have observed this trend (46,48,49,63). Findings from the present study confirm the need to inform medical regulatory bodies regarding the need to educate physicians on perinatal FA recommendations and how to best provide PCC. Although many physicians expressed a positive attitude toward their practice and perinatal recommendations, the reality is that there is a lack of routine prescribing of FA, particularly a lack in prescribing the correct recommended dose.

The SOGC guideline was first published in 1993 and has since undergone three revisions, which largely involve modifications to the three risk-category definitions. The evolution of the guidelines over time has led to some confusion and may be an underlying cause for the lack of knowledge exhibited by health care professionals. Responses to the open-ended questions of our survey conveyed physicians expressing that the guidelines were lengthy and confusing which may be a deterrence to staying up to date with them. Furthermore, multiple physicians noted that indeed a majority of available PVS in the marketplace contain 1 mg of FA, limiting their recommendations. This sentiment may explain why almost half of physicians chose "for no particular reason" when asked about the reason for the supplement they most often recommend. A majority of prenatal vitamin supplements are over-the-counter and thus, not

covered nor reimbursed by insurance companies. Prescribed supplements are only available at the 1.1 mg and 5 mg FA doses (33), which may reflect the pressure felt by some physicians to recommend higher than recommended doses in order to take into consideration women's preference and lower cost; both of which were the next most popular options. Finally, physicians are hesitant to recommend something that is not widely available nor labelled as prenatal. Most recently, Health Canada's multi-vitamin/mineral supplemental monograph was updated (September 25, 2018) to include an optional statement which aligns the allowable FA content with the recommended dose of FA which may lead to promising improvements in the future (64).

Undertaken in the National Capital Region, findings from the present study may not necessarily reflect a nationally representative sample of all Canadian physicians. The primary limitation to the generalization of the results is the sample being a small, self-selected convenience sample. The number of questions we were able to include to capture physicians' KAP limited the depth of data collected. On the other hand, a shorter completion time encouraged physicians to participate in the study, whom otherwise expressed little interest or time to participate. Our assessment of physicians' level of KAP regarding periconceptional FA may be skewed as more than half of participants were still in training or had been practicing for less than five years. Nonetheless, in light of concern over the unprecedented shift of Canadian pregnant women's folate status, our study is the first to assess the knowledge, attitude and practice of Canadian physicians regarding periconceptional FA. We are also the first to correlate physicians' KAP in addition to taking into consideration the misalignment concerning FA content in PVS.

4.6 Conclusion

The primary outcomes of the present study are in line with other studies emphasizing that continued educational programs and training in PCC and current evidence-based clinical practice guidelines is upmost imperative at this time to ensure optimal maternal and fetal health across the country. Although in line with current literature, the present findings indicate that examining this topic with a more pan-

Canadian random sampling could draw more nationally-representative conclusions. It is imperative that physicians across every province keep up to date to best inform their patients. Physicians are the linking bodies between expert guidelines and women, playing a large role in promoting the use of FA supplements. It is thus essential that physicians adopt the encouraged PCC recommendations to ensure optimal FA intake for all WCBA, particularly among disadvantaged groups of women. Future directions must include continued education of both health care professionals and consumers on harmonized recommendations of FA to increase the demand for products with the recommended dose.

4.7 Conflict of interest statement

The authors declare that there are no conflicts of interest.

4.8 Acknowledgement

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Table 1. Sociodemographic and professional practice characteristics of study participants (n= 77).

Variables	
Age, Mean ± SD	41.3±13.3
Gender *n* (%)	
Females	63 (81.8)
Males	14 (18.2)
Type of practice/ specialization, *n* (%)	
Family physician	48 (62.3)
Obstetrician-Gynecologist (OB-GYN)	16 (20.8)
Medical Resident	7 (9.1)
Medical Student	6 (7.8)
Primary place of employment, *n* (%)	
Hospital	25 (32.5)
Private practice (PP)	13 (16.9)
Family Health Team (FHT) or Family Health Organization (FHO)	21 (27.3)
Mixed	18 (23.4)
Hospital & PP	11 (14.3)
Hospital & FHT/FHO	4 (5.2)
PP & FHT/FHO	4 (5.2)
Number of years in professional practice, *n* (%)	
Still in training	18 (23.4)
<5 years	17 (22.1)
5-15 years	16 (20.8)
16-25 years	8 (10.4)
>25 years	18 (23.4)
Average number of nonpregnant, childbearing-aged women seen per week, *n* (%)	
0-15	35 (45.5)
16-30	28 (36.4)
31-50	9 (11.7)
> 50	5 (6.5)
Average number of pregnant women seen per week, *n* (%)	
0-15	51 (66.2)
16-30	14 (18.2)
31-50	9 (11.7)
> 50	3 (3.9)

Data presented are means±SD or frequencies as appropriate. *2 missing age values

Table 2. Knowledge, attitude and practice (KAP) scores of physicians regarding periconceptional folic acid recommendations, intake and health related outcomes.

Knowledge, Attitude and Practice (KAP) Scores	**Mean ± SD**	**Maximum Potential Score**
Total knowledge score (TKS)[a]	6.4 ± 1.7	17
Knowledge score of general and low risk factors for NTDs (KS1)	1.8 ± 1.2	8
Knowledge score of moderate and high risk factors for NTDs (KS2)	4.6 ± 1.2	9
Total attitude score (TAS)	18.0± 2.5	30
Total practice score (TPS)	2.04 ± 1.2	4

[a]TKS is the sum of KS1 and KS2. NTD = neural tube defects.

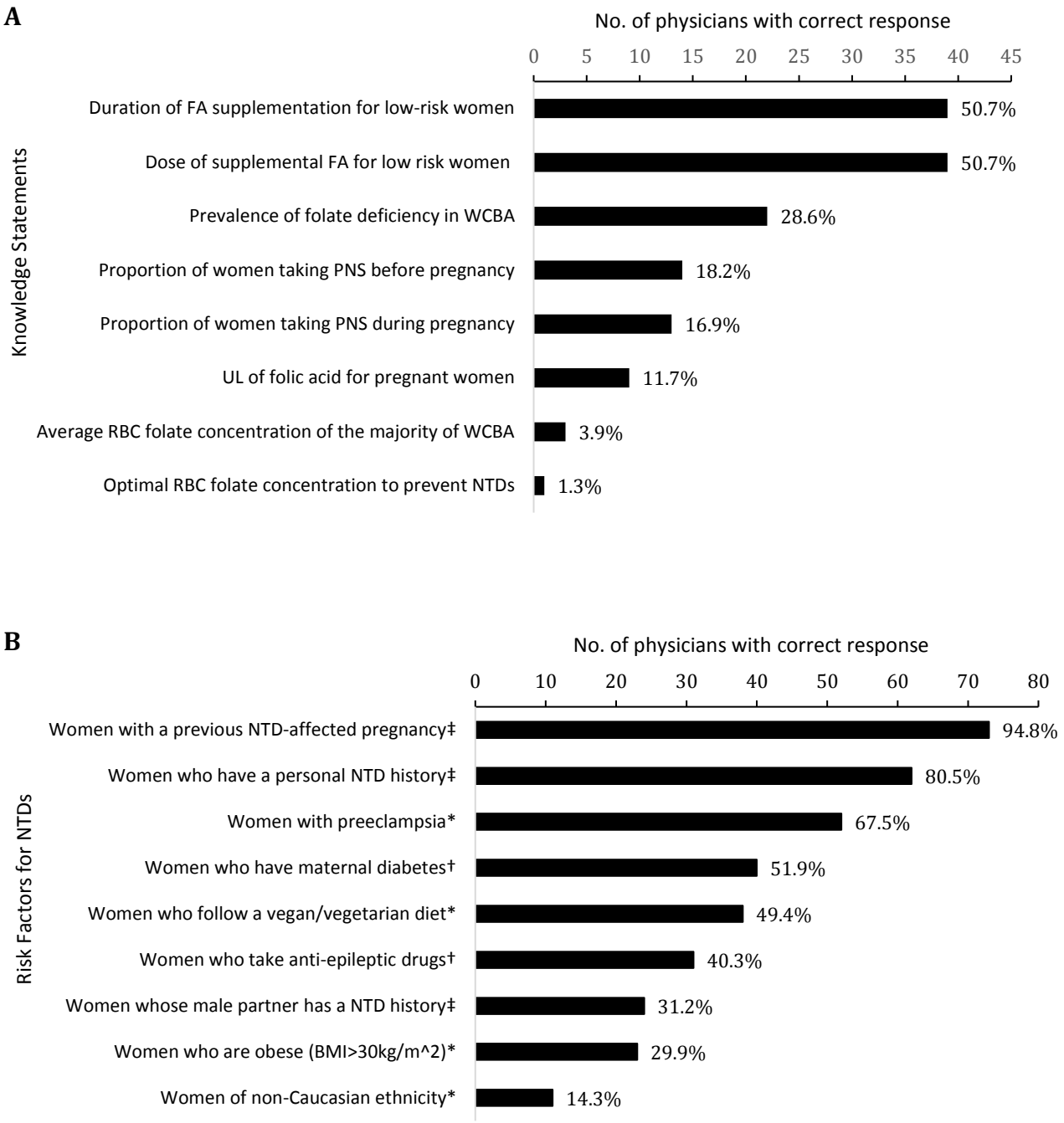

Figure 1. Physicians' knowledge regarding **(A)** periconceptional and perinatal FA recommendations, pregnant Canadian women's status, and health-related outcomes; and **(B)** moderate and high risk factors for neural tube defects (NTDs). Percentages indicate the correct response rate. WCBA=women of childbearing age; PVS=prenatal vitamin/mineral supplements; UL=tolerable upper intake level; RBC=red blood cell; BMI=body mass index expressed in units of kg/m^2, resulting from mass in kilograms and height in meters.

* Not a risk factor

† Moderate risk factor

‡ High risk factor

Table 3. Relationship between knowledge and attitude scores regarding folic acid supplement recommendations during pregnancy.

Statement	Attitude	n (%)	KS1	p-value	KS2	p-value	TKS	p-value
I am familiar with the most recent guideline	Agree	24 (31.2)	2.0 ± 0.24	0.42	4.8 ± 0.25	0.58	6.8 ± 0.34	0.35
	Unsure	25 (32.5)	1.6 ± 0.23		4.6 ± 0.25		6.2 ± 0.34	
	Disagree	28 (36.4)	1.8 ± 0.22		4.4 ± 0.24		6.3 ± 0.32	
There could be potential adverse effects due to high FA intake during pregnancy	Agree	21 (27.3)	2.0 ± 0.26	0.45	4.7 ± 0.27	0.57	6.6 ± 0.37	0.26
	Unsure	31 (40.3)	1.6 ± 0.21		4.4 ± 0.22		6.0 ± 0.30	
	Disagree	25 (32.5)	2.0 ± 0.23		4.8 ± 0.25		6.7 ± 0.34	
High FA intake may negatively modify fetal development	Agree	15 (19.5)	1.9 ± 0.30	0.87	4.6 ± 0.32	0.21	6.5 ± 0.44	0.54
	Unsure	36 (46.8)	1.75 ± 0.2		4.8 ± 0.21		6.6 ± 0.28	
	Disagree	26 (33.8)	1.8 ± 0.23		4.3 ± 0.24		6.2 ± 0.33	
Most PVS contain the recommended amount of FA	Agree	58 (75.3)	2.0 ± 0.14[a,c]	0.004	4.5 ± 0.16	0.42	6.6 ± 0.22	0.40
	Unsure	9 (11.7)	0.7 ± 0.37[a]		5.1 ± 0.41		5.8 ±0.56	
	Disagree	10 (13.0)	1.7 ± 0.35[b,c]		4.5 ± 0.4		6.2 ±0 .53	
My recommendations are in line with the most recent guideline	Agree	47 (61.0)	2.0 ± 0.17	0.32	4.6 ± 0.18	0.57	6.6 ± 0.25	0.65
	Unsure	28 (36.4)	1.6 ± 0.22		4.5 ± 0.24		6.2 ± 0.32	
	Disagree	2 (2.6)	1.0 ± 0.82		5.5 ± 0.88		6.5 ± 1.20	
I'm comfortable recommending PVS that are not in line with the guideline	Agree	12 (15.6)	1.9 ± 0.34	0.82	5.2 ± 0.35	0.19	7.1 ± 0.48	0.26
	Unsure	23 (29.9)	1.7 ± 0.25		4.4 ± 0.26		6.1 ± 0.35	
	Disagree	42 (54.6)	1.9 ± 0.18		4.5 ± 0.19		6.4 ± 0.26	

P values were estimated using general linear models with Tukey's post hoc test for subgroup comparisons. The letters indicate which attitude subgroups in response to statements were found to differ significantly. Subgroups with the same letters do not differ significantly while those with different letters do. FA= folic acid; KS1=sub-knowledge score 1; KS2=sub-knowledge score 2; PVS=prenatal vitamin/mineral supplement.

*The total knowledge score is the sum of knowledge sub-scores one and two and they are presented as means ±SE.

Table 4. Physicians' practice regarding folic acid supplement recommendations for low-risk women.

Practice Statement	n (%)
Which option best describes your clinical practice?	
I follow the guidelines, which are in line with most available PVS	41 (53.3)
I do not follow the guidelines because most PVS are not in line	2 (2.6)
I follow the guidelines and recommend non-PVS with correct FA-content	4 (5.2)
I do not follow the guidelines and recommend non-PVS regular supplements	1 (1.3)
I don't know	29 (37.7)
Supplement I most often recommend	
400 µg	23 (29.9)
1,000 µg	42 (54.6)
>1,000 µg	4 (5.2)
Any prenatal multivitamin supplement	8 (10.4)
Reason for recommendation	
I recommend a well-known brand name	2 (2.6)
Because of supplement composition/content	5 (6.5)
Because it is the women's preference	19 (24.7)
Because it is covered by many insurance companies	4 (5.2)
Because of lower cost	12 (15.6)
For no particular reason	35 (45.5)

*PVS=prenatal vitamin/mineral supplements; FA=folic acid.

Table 5. Comparison between mean total scores of knowledge, attitude and practice (KAP) by socio-demographic and professional practice characteristics of participants.

Variable	Groups of responses	Sub-knowledge score 1 (KS1)	*P*	Sub-knowledge score 2 (KS2)	*P*	Total knowledge score (TKS)	*P*	Attitude score (TAS)	P	Practice score (TPS)	*P*
Age	≤35 years	1.9±0.2	0.51	4.3±0.2	0.04	6.2±0.3	0.31	18.3±0.4	0.49	1.9±0.2	0.66
	>35 years	1.7±0.2		4.9±0.2		6.6±0.3		17.9±0.4		2.1±0.2	
Type of practice	Family physician	1.8±0.2	0.18	4.8±0.2	0.08	6.7±0.2	0.21	17.9±0.4	0.42	1.9±0.2	0.52
	OB-GYN	1.3±0.3		4.4±0.3		5.8±0.4		18.1±0.6		2.2±0.3	
	Medical resident	2.1±0.4		4.4±0.5		6.6±0.6		17.7±1.0		1.9±0.5	
	Medical student	2.3±0.5		3.5±0.5		5.8±0.7		19.7±1.0		2.7±0.5	
Place of employment	Hospital	1.9±0.2	0.61	4.6±0.3	0.71	6.5±0.3	0.39	17.5±0.5	0.13	1.9±0.3	0.69
	Private practice	2.0±0.3		4.9±0.3		7.0±0.5		19.3±0.7		2.0±0.3	
	FHT/FHO	1.9±0.3		4.6±0.3		6.4±0.4		17.6±0.5		2.0±0.3	
	Mixed	1.5±0.3		4.4±0.3		5.9±0.4		18.5±0.6		2.3±0.3	
Years of practice[b]	Still in training	2.0±0.3	0.14	4.1±0.3 [a]	0.004	6.1±0.4 [a]	0.002	19.0±0.6	0.38	2.0±0.3	0.66
	<5 years	1.4±0.3		4.5±0.3 [a]		5.9±0.4 [a]		17.8±0.6		1.8±0.3	
	5-15 years	1.4±0.3		4.3±0.3 [a]		5.8±0.4 [a]		17.8±0.6		1.9±0.3	
	16-25 years	2.1±0.4		5.9±0.4 [b]		8.0±0.5 [b]		18.4±0.9		2.5±0.4	
	>25 years	2.2±0.3		4.9±0.3 [a]		7.2±0.4 [a]		17.4±0.6		2.2±0.3	
Non-pregnant women seen per week	0-15	1.9±0.2	0.86	4.6±0.2	0.54	6.5±0.3	0.95	18.4±0.4	0.31	2.0±0.2	0.91
	16-30	1.9±0.2		4.4±0.2		6.3±0.3		17.7±0.5		1.9±0.2	
	31-50	1.6±0.4		5.1±0.4		6.7±0.6		18.4±0.8		2.1±0.4	
	> 50	1.6±0.5		4.8±0.6		6.4±0.8		16.4±1.1		2.4±0.6	
Pregnant women seen per week	0-15	1.9±0.2	0.32	4.6±0.2	0.56	6.6±0.2	0.60	18.3±0.4	0.60	1.9±0.2	0.06
	16-30	1.4±0.3		4.9±0.3		6.4±0.5		17.4±0.7		2.5±0.3	
	31-50	1.4±0.4		4.3±04		5.8±0.6		17.4±0.8		1.6±0.4	
	> 50	2.0±0.7		4.0±0.7		6.0±1.0		18.0±1.5		3.3±0.7	

P values were estimated using general linear model analyses and subgroup comparisons by Tukey's post hoc tests. The letters indicate which sociodemographic or professional practice were found to differ significantly. Subgroups with the same letters do not differ significantly while those with different letters do. OB-GYN=obstetrician-gynecologist; FHT=family health team; FHO=family health organization.

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Chapter 5: Discussion

5.1 Discussion

Pre-conception care is one of the most important components of health care for women in reproductive age that seeks to improve health outcomes by pregnancy risk-assessment, education, and diagnostic interventions. In the same way, physicians are the linking bodies between expert guidelines and women and thus, it is imperative that they keep up to date to best inform their patients. Physicians play an important role in promoting the use of FA supplements; thus, it is essential that physicians adopt the encouraged PCC recommendations to ensure optimal FA intake for all WCBA, particularly among disadvantaged groups of women. This study aimed to assess physicians' knowledge and attitude regarding the SOGC guidelines, FA intake and its health-related outcomes and furthermore, how that influences their practice. This study was designed to explore physicians' perceptions and barriers regarding the existing misalignment between FA supplement content and expert guidelines.

Results obtained in the present study showed that physicians had some knowledge of folic acid, including periconceptional prenatal vitamin supplement recommendations and health related topics, however, the lack of some knowledge possibly led to the relatively low rate of correct practicing behaviours. Our findings suggest that the two main factors that were associated with the rate of correct knowledge were the age of physicians and the number of years of professional practice. Regardless of the current state of KAP scores, a vast majority of physicians are either unsure or would not feel comfortable recommending a PVS that is not in line with current guideline recommendations.

Most surveys reported in the literature reveal a lack of physicians' knowledge regarding folic acid recommendations during pregnancy (199–203). Our study, however, is the first to conduct an assessment focused on physician's KAP regarding periconceptional FA recommendations in a Canadian setting. Previous studies that have investigated related topics, have primarily focused on health care professionals' knowledge, awareness and practice of FA in regard to its role in preventing NTDs

specifically. Unlike those studies, which took place in Ethiopia, Israel, India, the United States and China (199–203), our study's approach also took into consideration the growing concern over the shifting Canadian folate status and the misalignment.

The current literature exposes the insufficient level of physicians' knowledge regarding the correct dose and duration of FA-supplementation for the prevention of NTDs and our findings are in line with these conclusions. Two studies, performed by Demilew and Nigussie in Ethiopia (199) and Li et al. in China (203), were most comparable to ours in terms of population, assessment and outcomes of interest. Demilew and Nigussie's cross-sectional study assessed the knowledge and prescribing practice of FA of health professionals in Ethiopia (n=424) (199). This study also used eight item questions (yes or no response) to assess knowledge on FA, where a score of more than five was considered as "sufficient knowledge" and below five was considered as "insufficient knowledge". Our study's eight questions addressing general and low-risk recommendations focused on knowledge regarding the Canadian folate status and the correct dose and duration of supplementation while only one of Demilew and Nigussie's knowledge items addressed the recommended dose for low risk women and one for high risk. The other questions asked health professionals to confirm FA's role and relation to NTDs. Prescribing practices were assessed on whether respondents gave FA during the periconceptional period, counseled women on the benefits of FA and if they prescribed 4mg for high risk mothers. Similarly to our findings, approximately half of the sample had sufficient knowledge, however, few respondents knew the correct dose of FA for low-risk women and even less knew the appropriate dose to prevent recurrence. The Ethiopian study included nurses, midwives and general practitioners and similarly to the present study, half of their sample also had less than five years of work experience. They found that general practitioners were more knowledgeable and further, knowledge was significantly associated with age and having more work experience, specifically in antenatal care clinics (199). In a comparable way, Li et al. assessed the knowledge, attitude and practices related to FA supplements of 5,860 obstetricians and specialists in

women's health in China (203). The Chinese study showed that only 34.1% of all participants were aware of the need for women who can become or who are planning to become pregnant to take FA supplements, 34.3% knew the correct time to take FA, and 48.0% knew how to correctly give FA to women at risk of having infants with NTDs (203). In contrast to the Ethiopian study, which assessed a variety of health care professionals, Li et al.'s study participants only included doctors with specialized training to prevent birth defects in areas with a high incidence of NTDs. This may attribute to their slightly higher correct response rate for knowledge items (60.3%) and correctly answered questions about related practices and attitude (90%). Similarly to our study, a discrepancy was observed between physicians' KAP scores and their practicing behaviours in reality. Li et al. reported that only 77% of physicians routinely prescribed FA tablets to women planning to become pregnant while working, despite their high survey scores (203).

The depth-level of knowledge questions posed to the participants in the above-mentioned studies is critical to consider. Based on the questions included in their surveys, in comparison to ours, one can infer that our study's knowledge items assumed a higher caliber of base professional knowledge and thus, our questions were more in depth and specific to both the Canadian population and guideline recommendations. Both studies, in Ethiopia and China, assessed large samples of health professionals, using self-administered questionnaires. The present study, alike, confirmed similar findings among our smaller sample, particularly concerning FA recommendations for moderate and high risk women as well as the association between age and years of practice. Although a number of studies have addressed physicians' knowledge and practicing behaviours regarding folic acid, none of these studies have analyzed the link or potential correlation between physicians' knowledge, attitude and practice as well as its impact given the currently existing misalignment between FA-content in prenatal vitamin supplements and expert guidelines.

Although a majority of physicians are aware of FA's role in preventing NTDs, there is a lack of knowledge regarding the correct dose and duration of supplementation as well as FA-related health outcomes. Results from our study support those reported in the literature indicating that poor knowledge, which has been linked to poor practice behaviours in our study, are primarily due to a lack of knowledge resulting from the need for more educational resources to address this topic with physicians (204–206).

A majority of studies assessing physicians, whether it be their knowledge, attitude and/or practice, regardless of geographical location, possess an interesting commonality. A majority of respondents tend to be female, which is unexpected given the fact that it has been reported over the years that a majority of Canadian family physicians are male (207). However, the Physicians in Canada 2016 Summary Report highlighted that more recently, the number of female physicians continues to rise, with a 21% increase seen between 2012 and 2016 (207). These trends have also been observed in the US, where North America now can expect a majority (54%) of physicians under the age of 40 to be female (208). The mean age of participants in the present study was 41.3±13.3 years, however. Thus, it is possible that female physicians tend to be more willing to participate in research studies pertaining to pregnancy and women-related health topics. If this is the case, there may be other underlying factors relating to female physicians' practice that could skew the resulting observed levels of KAP as well.

Evidence from the literature indicates that, globally, women have poor or insufficient knowledge of folic acid (179,184,209). Several studies have also addressed the relationship between maternal sociodemographic factors and FA awareness, knowledge and use of folic acid (179,181–183,210,211). These studies have unanimously observed that a woman's educational status as well as overall socioeconomic standing, plays a critical role in FA knowledge and periconceptional use. In fact, low maternal education has long been found to be highly associated with neural tube defects in the US. Farley et al. conducted a population-based case control study of all live-born infants in Colorado from 1989 to

1998 (*n* = 551 285) (96). Statistically significant associations were found between NTDs and female sex of the child, lower maternal age, maternal country of birth in Mexico and maternal education less than tenth grade. The single strongest predictor of having a child with an NTD was low maternal education, however, which is well established as a strong marker for overall socioeconomic status, which is also significantly correlated to risk of a NTD-affected pregnancy (96,212). It has been well documented that poor North American women are less likely to be aware of the importance of folate or to take it preconceptionally (213–215). It is understood that these populations appear particularly vulnerable to not benefiting from the advantages of periconceptional folic acid, strongly emphasizing the importance of preconception care. This is especially true since approximately half of pregnancies in Canada are unplanned (187). The potential benefits of delivering PCC to WCBA were described by Reynolds in 1998, stating that if women were aware of their unhealthy lifestyles, they would change their behavior before, during and after their pregnancy, and the quality of life and general health of these women would rise (216). He also stated that there would be fewer unwanted pregnancies and pregnancy outcomes would improve by decreasing mortality and morbidity in both mother and child. This can be explained because PCC intervenes before the critical period of organogenesis rather than later in pregnancy. This has been concluded by several studies on the importance of providing PCC to all women who can become pregnant or that are pregnant (175,185,186,205,217).

Perinatal counselling is an approach that requires an open dialogue between the physician and the woman, to allow a better understanding of the user's knowledge, perceptions and lifestyle (185). The government of Canada and the SOGC guidelines alike, advise both women and physicians to take advantage of regular visits as an opportunity to identify health risks, offer related interventions and encourage positive health behaviours *prior* to conception (5,187). Regulatory bodies state that physicians should "recommend a daily multivitamin containing 400 µg of folic acid for all women of reproductive age who could become pregnant, and discuss risk factors that may warrant a higher dose" (5,187). Despite

this recommendation, several studies, including the present one, have observed physicians' lack of knowledge that is clearly reflected in poor prescribing practices in regard to FA during the periconceptional period as described above (199,200,203,218). There remains an urgency to change this trend since physicians are women's continued preferred source for preconception information (176). It seems like health practitioners agree to a large extent about the importance of PCC; however, globally, it seems that PCC is still not widely implemented nor practised. In the UK, Heyes et al. assessed the beliefs and attitudes of physicians, nurses and midwives regarding PCC (n=163) (219). Although respondents felt that PCC, including folic acid advice, is important to WCBA, it was not a high priority in their workload. Likewise, the findings from Kitamura et al.'s KAP study in Japan regarding PCC by family physicians and general practitioners (n=268) revealed that the most common education received was about smoking cessation and the least was about FA supplementation (220). In contrast, Lefebvre et al. reported that among 66 Canadian physicians, 92.3% answered folic acid questions correctly, compared to 82.0% for nicotine and 57.1% for alcohol (204). These two studies convey two points regarding physicians and poor PCC observed. Firstly, it is clear that there is a lack of education and training in PCC and secondly, there is a dire need to re-prioritize the importance of PCC within healthcare and medical school curriculums.

Findings from the present study confirm the need to inform medical regulatory bodies regarding the benefits of educating physicians on perinatal FA recommendations and on how to best provide PCC. Although many physicians expressed a positive attitude toward their practice and perinatal recommendations, the reality is that there is a lack of routine prescribing of FA, particularly a lack in prescribing the correct recommended dose depending on individual NTD-risk. Open-ended questions in the present study asked physicians about their perceptions and barriers regarding the misalignment between FA supplement content and recommendations. Multiple physicians expressed that the clinical practice guidelines are lengthy and confusing in addition to not being aware of the updated practice guideline. The SOGC guideline was first published in 1993 and has since undergone three revisions,

primarily involving changes in defining low, moderate and high risk women as well as minor changes in dose recommendations. Over the evolution of the guidelines, the current 2015 recommended dose have come full circle and are the same as those published in the first guidelines in 1993; however, these changes may be an underlying cause for confusion and the lack of knowledge exhibited by health care professionals. Some physicians mentioned the misalignment to be a source of difficulty in their ability to recommend appropriate prenatal vitamin supplements. However, this may have only been more obvious to respondents at the end of the questionnaire, once they were presented with the current recommendation because initially, 75.3% of physicians agreed that most PVS contain the recommended amount of FA. This finding only further contradicts the fact that cumulatively, 69% of physicians were not even familiar with the most recent guideline. Results from our study emphasize that, ultimately, physicians are confused and unfamiliar with the guidelines and that they most often recommend a PVS containing 1000 µg of FA because that is what is generally available in the marketplace. Furthermore, physicians are hesitant to recommend a product that is not widely accessible nor labelled as prenatal while trying to comply with the pressures of women's preference and lower cost associated to prescribed supplements that are only available at the 1.1 mg and 5 mg FA doses (50).

The foundation of this research study is a workshop that was held in Ottawa on November 17th, 2017, titled "Periconceptional intake of folic acid among low-risk women: Aligning prenatal supplement content with current expert guidelines". The overall goal of the workshop was to identify challenges and solutions to aligning supplemental FA intakes with current evidence-based recommendations. Thirty-eight (38) stakeholders from academia, industry, government, and healthcare professional groups participated. Group discussions facilitated the identification and prioritization of five key challenges for which solutions and implementation strategies were proposed. The five themes encompassed clarity and harmonization of evidence-based guidelines, reformulation or relabeling of FA-containing supplements, access to FA for all women, knowledge dissemination strategies and education of the public and health care professionals,

and attitude change to overcome the perception of "more is better" (50). The workshop aimed to align the FA-content in prenatal vitamin supplements with evidence-based recommendations through concerted effort of experts from various key stakeholder groups, including healthcare professionals. Identified as a having an impactful role in both industry and public health, the present study addressed physicians' role and stance in regard to the misalignment since their recommendations are influential to women and can drive the marketplace supply and demand.

Physicians have a unique positionality and are a key stakeholder group in ensuring the health of women, their babies and being capable to influence the pharmaceutical industry. Despite their influential power, there currently does not exist a widely available prenatal supplement containing 400 μg of FA for a physician to recommend. More recently, the workshop constituting the foundation of this study has had a rippling effect. Since it took place in 2017, Health Canada's multi-vitamin/mineral supplemental monograph was updated (September 25, 2018) which now aligns the allowable FA content with the recommended dose of FA (221). A monograph is a written standard that establishes product specifications such as name, packaging, storage and labelling requirements. Resulting from the update, the monograph now allows for an optional statement to be included on products providing at least 400 μg of folic acid per day (e.g. as a prenatal supplement). The following optional statement can now be included under the "Directions for use" section on products indicated as prenatal: "*400 mcg of folate per day is adequate for most women (to reduce the risk of neural tube defects). Consult a health care practitioner/health care provider/health care professional/doctor/physician to determine if you would benefit from additional folate before taking this product.*" The benefits of this initiative are twofold. Firstly, it should encourage the industry to move toward developing prenatal supplements that are in line with the recommendations and raise awareness among pregnant women and those of childbearing age regarding safe and optimal FA intake. This initiative, along with findings from this study will help encourage mitigation of the

misalignment that currently, inhibits everyone, both physicians and women, from adhering to the SOGC guidelines and more importantly, it prevents women from following public health recommendations.

The primary outcomes of the present study are in line with the literature emphasizing that continued educational programs and training in PCC and current evidence-based clinical practice guidelines is upmost imperative at this time to ensure optimal maternal and fetal health across the country. In order to observe a marked effect, it is crucial that appropriate means and strategies are undertaken to effectively reach target physician audiences. Focusing on traditional medical school curricula as well as continued professional development programs may be the most appropriate approach to reach physicians and help align their practice with expert guidelines.

5.2 Strengths and Limitations

Undertaken in the National Capital Region, findings from the present study may not necessarily reflect a nationally representative sample of all of Canada's physician population. This study may have limitations with regard to the principle instrument used for data collection; including, the length of the questionnaire and varying levels of question difficulty (multiple choice vs fill in the blank) which may have contributed to lowering knowledge scores. a. The number of questions we were able to include to capture physicians' knowledge, attitude and practice limited the depth of data collected; however, a short completion time encouraged physicians to participate in the study. The most significant challenge of the study was recruitment of physicians due to a lack of time and/or interest in participating. During recruitment, most clinic coordinators and physicians asked if it was possible to complete the questionnaire electronically. In order to retrieve physicians' accurate and current state of knowledge, the research design was firm regarding in person completion of questionnaires, where use of electronic devices or consultation with colleagues was prohibited. This allowed for a more accurate representation of physician's current KAP and stance on the misalignment. Although the need for in-person supervision

limited the total number of physicians sampled, all questionnaires were fully complete and used for analysis. For feasibility reasons and because we wanted to assess current KAP rather than change in KAP over time, a cross sectional study design was the most appropriate choice. It allowed us to assess and determine the prevalence of good answers to FA-related questions and how they are related to their attitude and practice. It also enabled us to identify associations between sociodemographic characteristic traits and KAP scores. The results are in line with current literature; however, the present findings indicate that examining this topic with a more pan-Canadian random sampling could draw more nationally-representative conclusions. In the future, sampling physicians across Canada using larger, random sampling methods would enable more power to compare subgroups of physicians as well as their personal characteristics and thus, explore potential differences between provinces. In reality, however, the feasibility of these types of studies given the low interest and time for research of physicians may deter researchers from conducting such studies. Alternatively, RCTs could be conducted in the future to test the effectiveness of academic-based perinatal health/PCC education programs for medical students and practicing professionals regarding the impacts of educational training and knowledge transfer activities on physicians' knowledge, attitude and practice regarding periconceptional folic acid recommendations.

This study has several strengths including the fact that it was led by an interdisciplinary team made up of researchers, a physician and a dietitian. The diverse range of expertise allowed better understanding of various professional and practical elements that strengthened the conceptualization and execution of the study. Secondly, it is the first Canadian study to assess physicians' KAP regarding periconceptional FA and addressing the existing misalignment. Finally, the educational seminars and packages delivered to physicians after participating served as immediate knowledge mobilization activities contributing to improved knowledge and awareness and consequently, practice.

5.3 Significance, Implications, and Future Plans

Our findings are relevant in the wake of prenatal vitamin supplements containing high doses of FA that are not in line with recommendations. These findings can be used to inform regulatory medical bodies about the lack of primary and continued education for physicians on preconception care. It could also serve to influence the pharmaceutical industry to move toward developing PVS that are in line with the recommendations and thus, result in subsequent change seen in the Canadian market. Presenting physicians' strong willingness to recommend a 400 µg supplement to the pharmaceutical industry could help break the cycle of selling PVS containing the UL or more and ultimately lead to the production of a reformulated or relabelled prenatal vitamin supplement. A widely accessible and affordable prenatal supplement would enable all those who may become pregnant to consume an optimal amount of FA depending on their risk category.

The workshop mentioned earlier has led to multiple downstream effects and subsequent knowledge mobilization initiatives in addition to the updated monograph. Firstly, the workshop proceedings have been published in the American Journal of Clinical Nutrition (50), the highest ranked original research journal in the field of nutrition. Over the past two years, the outcomes of the workshop have been presented at various national conferences, online medical education modules and hospital grand rounds. The workshop's participants understand the importance of raising awareness and educating health care professionals involved in perinatal care. They have taken initiative of their own and have also participated in the abovementioned knowledge transfer activities within their respective fields of expertise. Change in industry has already been observed, when Nestlé Nutrition made the informed decision to reformulate their Nestlé® Materna® prenatal multivitamin. They released a new formulation containing 600 µg of FA in comparison to the popular original formulation containing 1000 µg of FA. This change was brought directly because of an attendee, and key industry stakeholder who, is in support of the workshop initiatives.

Given the current state of evidence, future directions should include addressing the pressures of cost and lack of accessibility, patient compliance and women's preference. To do so, the industry could change the maximum allowable over-the-counter dose of FA in supplements to 400 µg, resulting in doses that are ≥400 µg, to be available by prescription only and thus, be covered by insurance companies. Reformulation should also be encouraged industry-wide to mitigate risk to companies who are the first to align dose with recommendations (50). Perhaps more in line with the current research project, it will be necessary to better educate both health care professionals and consumers on harmonized recommendations of FA to increase awareness, knowledge and the demand for products with the recommended dose. This could be accomplished by concurrently launching a national-wide campaign that would focus on dissemination of FA knowledge and consist of in-service education for all maternal child health clinics staff and patients. The Public Health Agency of Canada has unveiled a folic acid and NTD awareness initiative including website resources, a video, poster, fact sheet and infographic brochure to ensure that women are getting an optimal amount of FA (222). The impact of this initiative has not been measured; however, similar efforts have been shown to effectively raise awareness, knowledge and utilization of FA. For instance, Amitai et al. assessed the effects of a national wide FA campaign that was launched in Israel, concurrently with the issue of guidelines regarding FA supplementation for WCBA (210). The campaign focused on the dissemination of FA knowledge to health professionals and women using a health education kit that included articles, pamphlets and a magnetized reminder to take FA. Two years after it's launch, Amitai et al. found that the campaign had resulted in significant increases in awareness and correct knowledge (quadrupled), and a six fold increase in FA utilization (210). Similarly, Watson et al. measured the residual effect of a consumer-directed information campaign in Australia, confirming the efficacy of FA campaigns and their educational material (180). In 1996, prior to the intervention, 12.5% of women were aware of folate and NTDs. Four years later, the provision of printed educational material in the 1997 intervention showed that awareness of the association between folate

and NTD had increased to 30.2% and the portion of women with knowledge and use of foods with added folate doubled (180). The aforementioned studies confirm that a FA campaign could significantly improve the knowledge, awareness and use of FA among WCBA and health care providers, alike. Further, Rofail et al. conducted a literature review to examine factors contributing to the success of FA public health campaigns worldwide (223). The review identified incomplete outreach, prior awareness and knowledge, closeness to pregnancy, demographics and other personal characteristics as factors that impact consumption of FA following campaigns. This information can help identify target groups not currently reached by campaigns and used to design health promotion strategies accordingly. In order to reach larger populations, including women of lower socioeconomic status, Rofail et al. suggest culturally relevant and specific campaigning such as billboards depicting different ethnicities and age groups, and "shock tactic" campaigns (e.g., depicting children with NTDs and life with an NTD) as well as prospects such as combining folic acid and oral contraceptives (223). In addition, the Ottawa workshop identified potential solutions and implementation strategies that included a strong focus on strengthening and harmonizing the evidence on the effective dose and duration of FA supplementation. Finally, innovative marketing strategies should be adopted (e.g., front-of-package messaging or coupons on sanitary products; shelf information at the point of purchase) and online social media that target all women of childbearing age, not just those planning a pregnancy. FA recommendations could be packaged within an overall strategy targeting women about a healthy lifestyle and family planning. Ultimately, in addition to industry support, these actions could help mitigate the current misalignment and help shift current folate intakes and statuses to recommended ranges.

5.4 Statement of contribution

Liana Arielle Mida and Bénédicte Fontaine-Bisson are responsible for the study's conceptualization, methodology, survey design and formal analysis. Liana conducted all data collection with the help of Bénédicte Fontaine-Bisson at both Grand Round visits. We thank Dr. della Zazzera for his

hospital affiliations and help in coordinating Grand Round visitation. We thank Dr. Karen Phillips for her valuable guidance and expertise in regard to methodology and reviewing the questionnaire. Finally, we would also like to acknowledge Katrina El Asmar and Myriam Beaudry's assistance in recruitment as well as Carolina Soto's aid in data entry. Written reports were prepared by Liana and Bénédicte contributed to writing, reviewing and editing as well as all supervision of this study.

5.5 Conclusion

In summary, this is the first study to assess physicians' knowledge, attitude and practice regarding periconceptional folic acid in a Canadian context. Furthermore, it is the first to investigate the correlation between physician's knowledge, attitude and practice while addressing the current misalignment between expert guidelines and the FA content in prenatal vitamin supplements. The results of this study indicate that physicians lack knowledge of the guideline recommendations, especially in regard to moderate and high risk recommendations. The results showed that poor practice is correlated to low levels of knowledge, which was found to be significantly associated to physicians' age and years of practice. Finally, the present study confirms that a majority of physicians have a positive attitude toward the guidelines and would be willing to recommend a prenatal vitamin supplement containing 400 µg FA, that is in line with recommendations. Future directions should include education of both health care professionals and consumers on harmonized recommendations of FA to increase demand for products containing the recommended dose. Increased knowledge-dissemination and awareness will help improve clinical practice; subsequently, helping to ensure safe and effective folic acid intake among pregnant women and those of childbearing age across the country.

Appendices

Appendix A: University of Ottawa REB approval documents

02/05/2018

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-03-18-324
Titre du projet / Project Title	Recommendations for folic acid intake during pregnancy: knowledge, attitude, and practice of physicians.
Type de projet / Project Type	Thèse de maîtrise / Master's thesis
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	02/05/2018
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	01/05/2019

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Liana MIDA	École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences	Chercheur Principal / Principal Investigator
Bénédicte FONTAINE-BISSON	École des sciences de la nutrition / School of Nutrition Sciences	Superviseur / Supervisor
Vincent DELLA ZAZZERA	The Ottawa Hospital/Montfort Hospital	Co-chercheur / Co-investigator

Conditions spéciales ou commentaires / Special conditions or comments

550, rue Cumberland, pièce 154
Ottawa (Ontario) K1N 6N5 Canada

550 Cumberland Street, Room 154
Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

02/05/2018

Université d'Ottawa
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University of Ottawa
Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout événement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Riana MARCOTTE
Responsable d'éthique en recherche / Protocol Officer
Pour/For Daniel LAGAREC Président(e) du/ Chair of the Comité d'éthique de la recherche en sciences sociales et humanités / Social Sciences and Humanities Research Ethics Board

550, rue Cumberland, pièce 154 Ottawa (Ontario) K1N 6N5 Canada
550 Cumberland Street, Room 154 Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

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Canada's university

INFORMATION AND CONSENT FORM

Title of the Study: Recommendations for folic acid intake during pregnancy: Assessing the knowledge, attitude, and practice of physicians.

Principal Investigator
Bénédicte Fontaine-Bisson, RD, PhD
Associate Professor
School of Nutrition Sciences
Faculty of Health Sciences
University of Ottawa
(613) 562-5800

Co-investigator
Vincent della Zazzera, MD, FRCSC, OBS/GYN
Clinical Researcher at l'Institut du savoir Montfort; Montfort Hospital, Staff Physician, Department of Obstetrics & Gynecology; Associate Professor, Department of OB/GYN, University of Ottawa

Co-investigator
Liana A. Mida
Master's Student
Interdisciplinary School of Health Sciences
Faculty of Health Sciences
University of Ottawa

Invitation to Participate: You are invited to participate in the abovementioned research study, a Master's project conducted by Liana Mida who is being supervised by Dr. Bénédicte Fontaine-Bisson, in collaboration with Dr. Vincent della Zazzera.

Participation: If you wish to participate in this study, please complete the attached survey. Your decision to complete and return this survey will be interpreted as an indication of your consent to participate. The survey should take you approximately ten (10) minutes to complete. You do not have to answer any questions that you do not want to answer. Once you have completed the survey, please return it to a member of the research team on site.

Purpose of the Study: From this research, we wish to assess physicians' knowledge, attitude, and practice regarding Canadian recommendations for women's perinatal folic acid intake.

Benefits: After completion of the survey questionnaire, a seminar will be held to update you on the current state of evidence behind the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommendations and the folic acid status of Canadian women of childbearing age and those who are pregnant. During this time, light refreshments and snacks will be provided.

Confidentiality and Anonymity: You have the researcher's assurance that the information you share will remain strictly confidential and will be used solely for the purposes of this research. The only people who will have access to the research data are the research team members. Results will be published in pooled (aggregate) format. Anonymity is guaranteed since a random number will be attributed to your questionnaire and you will not be asked to provide your name.

Conservation of data: The data gathered from the survey will be compiled into the research database REDCap, which is housed on a completely secure server at the Montfort Hospital. Only authorized research team members will be allowed to access the database with a password using a password protected computer. Ten years after the end of data collection, all information will be destroyed from REDCap, while the questionnaires will be shredded.

Voluntary Participation: You are under no obligation to participate and if you choose to participate, you may refuse to answer questions that you do not want to answer. Completion and return of the questionnaire by you implies consent.

Information about the Study Results: The results of this study may be published in a scientific journal and presented at conferences. If you have any questions or require more information about the study itself, you may contact the researcher or her supervisor using the phone numbers or emails mentioned herein. If you have any questions with regards to the ethical conduct of this study, you may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5, tel.: (613) 562-5387 or ethics@uottawa.ca

Please keep this form for your records.

Thank you for your time and consideration.

Signature of the principal investigator and co-investigator (MSc student)

_____	_____	_____
Bénédicte Fontaine-Bisson	Liana A. Mida	Date

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Titre du projet: Recommandations relatives à la consommation d'acide folique durant la grossesse : Évaluer les connaissances, les attitudes et les pratiques des médecins.

Chercheuse principale
Bénédicte Fontaine-Bisson, DtP, PhD
Professeure agrégée
École des sciences de la nutrition
Faculté des sciences de la santé
Université d'Ottawa
(613) 562-5800

Co-chercheur
Vincent della Zazzera, MD, FRCSC, OBS/GYN
Chercheur clinicien à l'Institut de savoir Montfort; Hôpital Montfort, Médecin au Département d'obstétrique et de gynécologie; Professeur agrégé, Département d'OB/GYN,
Université d'Ottawa

Co-chercheuse
Liana A. Mida
Étudiante à la maîtrise
École interdisciplinaire des sciences de la santé
Faculté des sciences de la santé
Université d'Ottawa

Invitation à participer: Vous êtes invité(e) à participer au projet de recherche de maîtrise de Liana Mida, sous la supervision de la Dre Bénédicte Fontaine-Bisson, en collaboration avec le Dr Vincent della Zazzera.

Participation: Si vous acceptez de participer à cette étude, vous devrez compléter le sondage ci-joint. Votre décision de remplir et de remettre ce sondage sera interprétée comme une indication de votre consentement à participer. Le sondage devrait vous prendre environ dix (10) minutes à remplir. Vous n'êtes pas obligé de répondre aux questions si vous ne voulez pas y répondre. Une fois le sondage complété, veuillez le retourner à un membre de l'équipe de recherche sur place.

But de l'étude: À l'aide de ce projet de recherche, nous souhaitons évaluer les connaissances, les attitudes et les pratiques des médecins en ce qui concerne les recommandations canadiennes relatives à la consommation périnatale d'acide folique chez les femmes.

Avantages: Après avoir rempli le sondage, un séminaire vous sera présenté concernant les recommandations de la Société des obstétriciens et gynécologues du Canada (SOGC) et le statut en acide folique des Canadiennes en âge de procréer et de celles qui sont enceintes. Pendant ce temps, des rafraîchissements et des collations seront servis.

Confidentialité et anonymat: Vous avez l'assurance des chercheurs que l'information que vous partagerez avec son équipe restera strictement confidentielle et sera utilisée uniquement aux fins de cette recherche. Les seules personnes qui auront accès aux données sont les membres de l'équipe de recherche. Les résultats seront publiés en format agrégé. Votre anonymat est garanti par l'utilisation d'un chiffre aléatoire qui aura été attribué à votre questionnaire. Vous n'aurez pas à fournir votre nom sur le questionnaire.

Conservation des données: Les informations recueillies seront compilées en ligne de manière entièrement sécurisée dans la base de données RedCap hébergée sur un serveur de l'Hôpital Montfort. Seuls les membres autorisés de l'équipe de recherche pourront y accéder avec un mot de passe sur un ordinateur protégé par un mot de passe. Enfin, dix ans après la fin de la collecte de données, les informations seront complètement effacées de la base de données RedCap, tandis que les questionnaires seront détruits à la déchiqueteuse.

Participation volontaire: Vous êtes entièrement libre de décider de participer ou non à cette étude. Si vous participez, vous pouvez refuser de répondre aux questions auxquelles vous ne souhaitez pas répondre. La complétion et la remise du questionnaire impliquent votre consentement.

Communication des résultats: Les résultats de cette étude pourraient être publiés dans des revues scientifiques ou présentés à des congrès. Pour tout renseignement additionnel concernant cette étude, vous pouvez communiquer avec notre équipe de chercheurs par téléphone ou par courriel tel que mentionné dans de document. Pour tout renseignement sur les aspects éthiques de cette étude, vous pouvez vous adresser au Comité d'éthique de la recherche de l'Université d'Ottawa par téléphone au 613-562-5387, par courriel à ethics@uottawa.ca ou en vous présentant en personne au 550 rue Cumberland, pièce 154, Ottawa K1N 6N5.

S'il vous plaît, gardez ce formulaire pour vos dossiers. Merci pour votre temps et votre considération.

Signatures de la chercheuse principale et de la co-chercheuse (étudiante à la maîtrise)

_____	_____	_____
Bénédicte Fontaine-Bisson	Liana A. Mida	Date

Telephone or Email Recruitment Script

Family Health Team

Hi,

My name is (name here) and I am a Master's student (or research assistant) at the University of Ottawa involved in the research project assessing physicians' knowledge, attitude, and practicing behaviours regarding perinatal intake of folic acid.

> **We would like to offer** the physicians from your FHT/clinic a free educational seminar regarding the current folate status of Canadian women and an updated overview of the 2015 SOGC guidelines regarding pre-conception folic acid and multivitamin supplementation.
>
> > **We would take this opportunity to ask them to answer a short survey as part of our research project.**
> >
> > **In brief**, we want to explore physicians' current state of knowledge and attitude toward the Society of Obstetricians and Gynecologists (SOGC) guidelines, folic acid intake, and its health-related outcomes during the perinatal period. Equally, we wish to learn how the knowledge and attitude influence their clinical practice.

I will be happy to answer your questions and give you more information on the nature of your participation in our study.

(Wait for their response….)

Is there a regularly scheduled staff meeting I could drop by for during the months of [complete as appropriate]?

(Wait for their response….)

I am inquiring/wondering if it can be arranged for me to come in (with one assistant potentially) for approximately 30 minutes. We would first distribute a survey questionnaire that will take approximately 10 minutes to complete. Once all surveys have been collected from the physicians, I (the Master's student) will then deliver a seminar presentation that will endure no longer than 20 minutes.

> Inquire how many (#) physicians are affiliated to the FHT/clinic and how many physicians, on average, we should expect to attend the "meeting".
>
> Inquire if the facility has a designated room in which we can have physicians fill out the questionnaire and hold the presentation in afterward. Please ask if this room has an appropriate computer/screen/projector available or a blank wall we could use for projection (bring our own projector if they do not have).

Montfort Voicemail to contact us/leave a message:

613-746-4621 *ext. 6028

If they say no to all staff meetings or arrangement options, the Master's student will thank them for their time.

Hospital

Hi,

My name is (name here) and I am the a Master's student (or research assistant) at the University of Ottawa involved in the research project assessing physicians' knowledge, attitude, and practicing behaviours regarding perinatal recommendations and intake of folic acid.

> **Here is a brief description of the project**: we want to explore physicians' current state of knowledge and attitude toward the Society of Obstetricians and Gynecologists (SOGC) guidelines, folic acid intake, and its health-related outcomes during the perinatal period. Equally, we wish to learn how the knowledge and attitude influence their clinical practice.
>
> **The benefits of participating in this study include** all physicians receiving an educational seminar regarding the current folate status of Canadian women and an updated overview of the 2015 SOGC guidelines regarding pre-conception folic acid and multivitamin supplementation.

I will be happy to answer your questions and give you more information on the nature of your participation in our study.

(Wait for their response….if email – ask they if/when we can contact them for more information)

I am inquiring if it can be arranged for members of our research team to come in to take up 30-40 minutes of a weekly Grand Round during the months of [complete as appropriate]. We would first distribute a survey questionnaire that will take approximately 10 minutes to complete. Once all surveys have been collected from the physicians, we will then deliver a seminar presentation that will last no longer than 20 minutes.

In order to survey the hospital's physicians, I am wondering if there is a weekly Grand Round that would be best for me to come to?

(Wait for their response….)

If they say no to all Grand Round arrangements, ask if there would be other opportunities to distribute our questionnaire and present our seminar.

Participant code: _____

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QUESTIONNAIRE

We thank you for taking part in this survey assessing physicians' knowledge, attitudes, and practices regarding Canadian recommendations for women's perinatal folic acid intake. This survey should take approximately 10 minutes to complete. **Please answer the questions in the order that they appear.** Note that many questions relate to the 2015 clinical practice guideline of the Society of Obstetricians and Gynecologists of Canada (SOGC).

GENERAL CHARACTERISTICS

1) Please indicate today's date: _____
   Day / Month / Year

2) Please indicate your age: _____ (years)

3) Please indicate your gender identity:
   - ☐ Female
   - ☐ Male
   - ☐ Neither/Non-binary
   - ☐ You don't have an option that applies to me. I identify as (please specify) _____

4) Please indicate your type of practice or specialization:
   - ☐ Family physician
   - ☐ Obstetrician-Gynecologist
   - ☐ Surgeon
   - ☐ Medical Resident
   - ☐ Other, please specify: _____

5) Please indicate your primary place of employment (can check more than one answer):
   - ☐ Hospital
   - ☐ Private practice
   - ☐ Family Health Team
   - ☐ Other, please specify: _____

6) Please indicate your number of years in professional practice (post training – e.g., after your residency):
   - ☐ Still in training
   - ☐ <5 years
   - ☐ 5-15 years
   - ☐ 16-25 years
   - ☐ >25 years

7) Please indicate on average the number of nonpregnant, childbearing-aged women seen per week:
   - ☐ 0-15
   - ☐ 16-30
   - ☐ 31-50
   - ☐ > 50

8) Please indicate on average the number of pregnant women seen per week:
   - ☐ 0-15
   - ☐ 16-30
   - ☐ 31-50
   - ☐ > 50

9) What is the prevalence of folate deficiency in reproductive-aged women in Canada?
   - ☐ 0-20%
   - ☐ 21-40%
   - ☐ 41-60%
   - ☐ 61-80%
   - ☐ >80%
   - ☐ I don't know

10) What is the optimal red blood cell folate concentration required for maximal protection from neural tube defects (NTDs)?
   - ☐ ≥320 nmol/L
   - ☐ ≥640 nmol/L
   - ☐ ≥906 nmol/L
   - ☐ I don't know

11) On average, the majority of Canadian childbearing aged women have red blood cell folate concentrations that:
   - ☐ meet the deficiency cut-off
   - ☐ meet the minimal cut-off for maximal protection against NTDs
   - ☐ are higher than required for maximal protection against NTDs.
   - ☐ I don't know

12) The Tolerable Upper Intake Level (UL) (maximum daily intake unlikely to cause adverse health effects) of folic acid for pregnant women is:
   - ☐ 1,000 µg
   - ☐ 5,000 µg
   - ☐ 10,000 µg
   - ☐ There is no established UL for folic acid during pregnancy.
   - ☐ I don't know

13) According to the 2015 SOGC guidelines, women with a low risk for a NTD affected pregnancy should consume:

- ☐ daily oral multivitamin supplement containing folic acid for at least 2-3 months before conception.
- ☐ daily oral multivitamin supplement containing folic acid for at least 2-3 months before conception, throughout pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues.
- ☐ daily oral multivitamin supplement containing folic acid for at least 6 months before conception and throughout pregnancy.
- ☐ daily oral multivitamin supplement containing folic acid for at least 2-3 months before conception and throughout the first three months of pregnancy.

14) What is the 2015 SOGC daily recommended intake of folic acid from supplements for women at low risk for a NTD affected pregnancy?

- ☐ 400 µg
- ☐ 600 µg
- ☐ 1,000 µg
- ☐ 5,000 µg
- ☐ I don't know

15) What proportion of Canadian women take prenatal supplements before pregnancy in the periconceptional period?

- ☐ 0-20%
- ☐ 21-40%
- ☐ 41-60%
- ☐ 61-80%
- ☐ 81-100%
- ☐ I don't know

16) What proportion of Canadian women take prenatal supplements during pregnancy?

- ☐ 0-20%
- ☐ 21-40%
- ☐ 41-60%
- ☐ 61-80%
- ☐ 81-100%
- ☐ I don't know

17) Please, fill-in-the blank with the amount (in µg) of folic acid required from a daily multivitamin supplement by women at moderate OR high risk of having a baby with a NTD.

- ☐ Women at **moderate** risk should take ____ µg before conception until 12 weeks of gestation and then continue with ____ µg.
- ☐ Women at **high** risk should take ____ µg before conception until 12 weeks of gestation and then continue with ___ µg.
- ☐ I don't know

18) According to the 2015 SOGC guidelines, which of the following options describe personal or co-morbidity conditions for women at <u>moderate OR high risk</u> of having a baby with a neural tube defect (NTD), for example spina bifida? (select all that apply)

Potential risk factors	Not a risk factor	Moderate risk factor	High risk factor
Women who have a personal NTD history			
Women who have had a previous pregnancy affected by an NTD			
Women of non-Caucasian ethnicity (e.g., Latino/Hispanic, East Asian, etc.)			
Women whose male partner has a NTD history			
Women with preeclampsia			
Women who take anti-epileptic drugs			
Women who have maternal diabetes			
Women who follow a vegan/vegetarian diet			
Women who are obese (BMI>30)			

19) I am familiar with the most recent SOGC clinical practice guidelines (2015):

☐ ☐ ☐ ☐ ☐

Strongly agree Agree Unsure Disagree Strongly disagree

20) I have heard/read that there could be potential adverse health outcomes due to high folic acid intake during pregnancy.

☐ ☐ ☐ ☐ ☐

Strongly agree* Agree* Unsure Disagree Strongly disagree

*Which one(s): _____

21) High folic acid intake during pregnancy may have a negative impact on fetal development.

☐ ☐ ☐ ☐ ☐

Strongly agree Agree Unsure Disagree Strongly disagree

22) Most prenatal supplements contain the recommended amount of folic acid, as stated in the 2015 SOGC guidelines.

☐ ☐ ☐ ☐ ☐

Strongly agree Agree Unsure Disagree Strongly disagree

23) I most often recommend a supplement containing _____ µg of folic acid to women at low risk for an NTD affected pregnancy:

- ☐ 400 µg
- ☐ 800 µg
- ☐ 1,000 µg (eg: Materna™)
- ☐ >1,000 µg (eg: Pregvit™ & Pregvit5™)
- ☐ Any prenatal multivitamin supplement
- ☐ Any regular multivitamin supplement
- ☐ Other: _____

24) What factors influence your choice of recommended supplement?

- ☐ I recommend a well-known brand name
- ☐ Because of sponsor/affiliation/arrangement with my workplace
- ☐ Because it is the women's preference
- ☐ Because it is covered by many insurance companies
- ☐ Because of lower cost
- ☐ For no particular reason
- ☐ Other: _____

25) My recommendations to women at low risk for NTDs are in line with the 2015 SOGC guidelines.

☐	☐	☐	☐	☐
Strongly agree	Agree	Unsure	Disagree	Strongly disagree

26) I am/would be comfortable prescribing prenatal supplements that are not in line with the 2015 SOGC recommendations?

☐	☐	☐	☐	☐
Strongly agree	Agree	Unsure	Disagree	Strongly disagree

27) Which of the following options best describes your clinical practice?

- ☐ I follow the 2015 SOGC guidelines which are in line with the most common prenatal supplement(s) on the market.
- ☐ I do not follow the 2015 SOGC guidelines because most prenatal supplements on the market do not align with them.
- ☐ I follow the 2015 SOGC guidelines and recommend supplements that are not marketed/labelled as "prenatal".
- ☐ I do not follow the 2015 SOGC guidelines and recommend supplements that are not marketed/labelled as "prenatal".
- ☐ I don't know

Participant code: _____

Here is a statement taken from the 2015 SOGC clinical practice guidelines (Please do not change your previous answers):

- Women with a low risk for a neural tube defect or other folic acid-sensitive congenital anomaly and a male partner with low risk require a daily oral multivitamin supplement containing *400 µg of folic acid for at least 2 to 3 months before conception, throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues.*

Based on these recommendations:

28) Do you practice according to the recommendations with regards to dose and duration of folic acid supplementation?

Dose (400 µg)
- ☐ Yes
- ☐ No

Duration
- ☐ Yes
- ☐ No

29) Would/do you feel comfortable practising according to the 2015 SOGC guidelines and recommending 400 µg?

☐	☐	☐	☐	☐
Strongly agree	Agree	Unsure	Disagree	Strongly disagree

30) Do you perceive that there is a misalignment between the 2015 SOGC recommendations and your ability to adhere to them? (Please explain)

_____
_____
_____
_____

31) Are there any barriers or challenges to follow the 2015 SOGC guideline recommendations regarding folic acid supplementation for women at low risk for NTDs? (Please explain)

_____
_____
_____
_____

32) Is there anything you would like to add with regards to your knowledge, attitude, and practice as it relates to folic acid intake before/during pregnancy?

_____
_____
_____

Code du participant: _____

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L'Université canadienne
Canada's university

QUESTIONNAIRE

Nous vous remercions de participer à ce sondage évaluant les connaissances, attitudes et pratiques des médecins relatives aux recommandations canadiennes pour la consommation d'acide folique périnatal chez les femmes. Ce sondage devrait prendre environ 10 minutes à compléter. **S'il vous plaît, veuillez répondre selon l'ordre dans lequel apparaissent les questions.** Veuillez noter que plusieurs questions sont reliées aux lignes directrices pour la pratique clinique de la Société des obstétriciens et gynécologues du Canada (SOGC) de 2015.

CARACTÉRISTIQUES GÉNÉRALES

1) Veuillez indiquer la date d'aujourd'hui: _____
Jour/ Mois / Année

2) Veuillez indiquer votre âge : _____ (années)

3) Veuillez indiquer votre identité de genre:
- ☐ Femme
- ☐ Homme
- ☐ Aucun/Non binaire
- ☐ Vous n'avez pas d'option qui s'applique à moi. Je m'identifie comme (veuillez préciser) _____

4) Veuillez indiquer votre type de pratique ou spécialisation:
- ☐ Médecin de famille
- ☐ Gynécologue-Obstétricien
- ☐ Chirurgien
- ☐ Résident en médecine
- ☐ Autre, veuillez préciser: _____

5) Veuillez indiquer votre lieu principal de travail (vous pouvez choisir plus d'une réponse):
- ☐ Hôpital
- ☐ Pratique privée
- ☐ Équipe de santé familiale
- ☐ Autre, veuillez préciser: _____

6) Veuillez indiquer le nombre d'années de pratique professionnelle (après la formation – ex. après votre résidence en médecine):
- ☐ Encore en formation
- ☐ <5 ans
- ☐ 5-15 ans
- ☐ 16-25 ans
- ☐ >25 ans

7) Veuillez indiquer, en moyenne, le nombre de femmes en âge de procréer qui ne sont pas enceintes que vous voyez par semaine:
   - ☐ 0-15
   - ☐ 16-30
   - ☐ 31-50
   - ☐ > 50

8) Veuillez indiquer, en moyenne, le nombre de femmes enceintes que vous voyez par semaine:
   - ☐ 0-15
   - ☐ 16-30
   - ☐ 31-50
   - ☐ > 50

9) Quelle est la prévalence de déficience en folate chez les femmes en âge de procréer au Canada?
   - ☐ 0-20%
   - ☐ 21-40%
   - ☐ 41-60%
   - ☐ 61-80%
   - ☐ >80%
   - ☐ Je ne sais pas

10) Quelle est la concentration optimale de folate dans les globules rouges sanguins requise pour une protection maximale contre des anomalies du tube neural (ATN)?
   - ☐ ≥320 nmol/L
   - ☐ ≥640 nmol/L
   - ☐ ≥906 nmol/L
   - ☐ Je ne sais pas

11) En moyenne, la majorité des femmes canadiennes en âge de procréer ont des concentrations de folate dans les globules rouges sanguins qui:
   - ☐ atteignent le seuil de déficience.
   - ☐ atteignent le seuil minimal pour une protection maximale contre les ATN.
   - ☐ sont plus élevées que nécessaire pour une protection maximale contre les ATN.
   - ☐ Je ne sais pas

12) L'apport maximal tolérable (AMT) (l'apport quotidien maximal qui n'est pas susceptible de causer des effets indésirables pour la santé) pour l'acide folique chez les femmes enceintes est:
   - ☐ 1,000 µg
   - ☐ 5,000 µg
   - ☐ 10,000 µg
   - ☐ Il n'y a pas d'AMT établi pour l'acide folique pendant la grossesse.
   - ☐ Je ne sais pas

13) Selon les lignes directrices de la SOGC de 2015, les femmes ayant un faible risque d'ATN devraient consommer un:

- ☐ supplément quotidien oral de multivitamines contenant de l'acide folique pendant au moins 2-3 mois avant la conception.
- ☐ supplément quotidien oral de multivitamines contenant de l'acide folique pendant au moins 2-3 mois avant la conception, pendant la grossesse et pendant 4 à 6 semaines après l'accouchement ou tout au long de l'allaitement.
- ☐ supplément quotidien oral de multivitamines contenant de l'acide folique pendant au moins 6 mois avant la conception et tout au long de la grossesse.
- ☐ supplément quotidien oral de multivitamines contenant de l'acide folique pendant 2-3 mois avant la conception et pendant les trois premiers mois de la grossesse.

14) Quel est l'apport quotidien d'acide folique provenant de suppléments recommandé par la SOGC de 2015 pour les femmes à faible risque d'une grossesse affectée par une ATN?

- ☐ 400 µg
- ☐ 600 µg
- ☐ 1,000 µg
- ☐ 5,000 µg
- ☐ Je ne sais pas

15) Quelle proportion de femmes canadiennes prennent des suppléments prénataux avant la grossesse, pendant la période préconceptionnelle?

- ☐ 0-20%
- ☐ 21-40%
- ☐ 41-60%
- ☐ 61-80%
- ☐ 81-100%
- ☐ Je ne sais pas

16) Quelle proportion de femmes canadiennes prennent des suppléments prénataux pendant la grossesse?

- ☐ 0-20%
- ☐ 21-40%
- ☐ 41-60%
- ☐ 61-80%
- ☐ 81-100%
- ☐ Je ne sais pas

17) Veuillez remplir les espaces avec la quantité requise (en µg) d'acide folique provenant d'un supplément de multivitamines quotidien pour les femmes à risque modéré OU élevé d'avoir un bébé avec une ATN.

- ☐ Les femmes à risque **modéré** devraient prendre _____ µg avant la conception jusqu'à 12 semaines de grossesse, puis continuer avec _____ µg.
- ☐ Les femmes à risque **élevé** devraient prendre _____ µg avant la conception jusqu'à 12 semaines de grossesse, puis continuer avec_____ µg.
- ☐ Je ne sais pas

Code du participant: _____

18) Selon les lignes directrices de la SOGC de 2015, lesquelles des options suivantes décrivent des conditions personnelles ou de comorbidité pour les femmes à risque modéré OU élevé d'avoir un bébé atteint d'une anomalie du tube neural (ATN), par exemple le spina bifida? (Sélectionnez toutes celles qui s'appliquent)

Facteurs de risque potentiel	**Pas un facteur de risque**	**Facteur de risque modéré**	**Facteur de risque élevé**
Les femmes qui ont une histoire personnelle d'ATN			
Les femmes qui ont eu une grossesse précédente affectée par une ATN			
Les femmes d'ethnicité non caucasienne (ex. Hispanique, Asiatique de l'Est, etc.)			
Les femmes dont le partenaire masculin a un historique d'ATN			
Les femmes avec prééclampsie			
Les femmes qui prennent des médicaments antiépileptiques			
Les femmes qui ont le diabète maternel (type I ou II)			
Les femmes qui suivent une diète végétalienne/végétarienne			
Les femmes qui sont obèses (IMC>30)			

19) Je suis familier/ère avec les plus récentes lignes directrices de pratique clinique de la SOGC (2015):

☐ ☐ ☐ ☐ ☐

Fortement d'accord D'accord Incertain(e) En désaccord Fortement en désaccord

20) J'ai entendu/lu qu'il pourrait y avoir des effets indésirables pour la santé dus à une consommation élevée d'acide folique pendant la grossesse.

☐ ☐ ☐ ☐ ☐

Fortement d'accord* D'accord* Incertain(e) En désaccord Fortement en désaccord

*Lequel ou lesquels: _____

21) Une consommation élevée d'acide folique pendant la grossesse pourrait avoir un impact négatif sur le développement du fœtus.

☐ ☐ ☐ ☐ ☐

Fortement d'accord D'accord Incertain(e) En désaccord Fortement en désaccord

22) La plupart des suppléments prénataux contiennent la quantité recommandée d'acide folique, comme qu'indiqué dans les lignes directrices de la SOGC de 2015.

☐ ☐ ☐ ☐ ☐

Fortement d'accord D'accord Incertain(e) En désaccord Fortement en désaccord

23) La plupart du temps, je recommande un supplément contenant _____ µg d'acide folique aux femmes à faible risque de grossesse affectée par une ATN:

- ☐ 400 µg
- ☐ 800 µg
- ☐ 1,000 µg (e.g.: Materna™)
- ☐ >1,000 µg (e.g.: Pregvit™ & Pregvit5™)
- ☐ N'importe quel supplément prénatal de multivitamines.
- ☐ N'importe quel supplément régulier de multivitamines.
- ☐ Autre: _____

24) Quels facteurs influencent votre choix de supplément recommandé?

- ☐ Je recommande un supplément de marque bien connue.
- ☐ En raison de commanditaires/affiliations/ententes à mon lieu de travail.
- ☐ En raison de la préférence des femmes.
- ☐ Parce qu'il est couvert par plusieurs compagnies d'assurance.
- ☐ Parce qu'il est moins dispendieux
- ☐ Pour aucune raison particulière
- ☐ Autre: _____

25) Mes recommandations pour les femmes à faible risque d'ATN sont conformes aux lignes directrices de la SOGC de 2015.

☐	☐	☐	☐	☐
Fortement d'accord	D'accord	Incertain(e)	En désaccord	Fortement en désaccord

26) Je suis/serais à l'aise de prescrire des suppléments prénataux qui ne sont pas conformes aux recommandations de la SOGC de 2015?

☐	☐	☐	☐	☐
Fortement d'accord	D'accord	Incertain(e)	En désaccord	Fortement en désaccord

27) Lequel des énoncés décrit le mieux votre pratique clinique?

- ☐ Je respecte les lignes directrices de la SOGC de 2015 qui concordent avec la plupart des suppléments prénataux les plus courants sur le marché.
- ☐ Je ne respecte pas les lignes directrices de la SOGC de 2015 puisque la plupart des suppléments prénataux sur le marché ne concordent pas avec celles-ci.
- ☐ Je respecte les lignes directrices de la SOGC de 2015 et recommande les suppléments qui ne sont pas commercialisés/étiquetés «prénataux».
- ☐ Je ne respecte pas les lignes directrices de la SOGC de 2015 et recommande des suppléments qui ne sont pas commercialisés/étiquetés comme « prénataux ».
- ☐ Je ne sais pas

Code du participant: _____

Voici un énoncé tiré des lignes directrices pour la pratique clinique de la SOGC de 2015 (veuillez ne pas changer vos réponses précédentes s.v.p.):

- Les femmes à faible risque d'anomalie du tube neural ou d'autre anomalie congénitale reliée à l'acide folique et ayant un partenaire masculin à faible risque, requièrent un supplément oral quotidien de multivitamines contenant *400 µg d'acide folique pendant au moins 2 à 3 mois avant la conception, pendant la grossesse, et pendant 4 à 6 semaines après l'accouchement ou tout au long de l'allaitement.*

Selon ces recommandations:

28) Votre pratique est-elle conforme aux recommandations concernant la dose et la durée de la supplémentation en acide folique?

Dose (400 µg)	Durée
☐ Oui	☐ Oui
☐ Non	☐ Non

29) Êtes/seriez-vous à l'aise de pratiquer selon les recommandations de la SOGC de 2015 et recommander 400 µg?

☐	☐	☐	☐	☐
Fortement d'accord	D'accord	Incertain(e)	En désaccord	Fortement en désaccord

30) Percevez-vous un décalage entre les recommandations de la SOGC de 2015 et votre capacité à les respecter? (S'il vous plaît, expliquez)

_____
_____
_____
_____

31) Y a-t-il des barrières ou des défis vous empêchant de suivre les recommandations de la SOGC de 2015 concernant la supplémentation en acide folique pour les femmes à faible risque d'ATN? (S'il vous plaît, expliquez)

_____
_____
_____
_____

32) Y a-t-il autre chose que vous aimeriez ajouter en ce qui concerne vos connaissances, votre attitude et votre pratique en lien avec la consommation d'acide folique avant /pendant la grossesse?

_____
_____
_____
_____

Appendix B: The Ottawa Hospital REB approval documents

The Ottawa Hospital | L'Hôpital d'Ottawa
RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

uOttawa

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Date:	September 24, 2018
To:	Dr. Vincent della Zazzera, University of Ottawa
Protocol ID:	20180540-01H
Study Title:	Recommendations for folic acid intake during pregnancy: knowledge, attitude, and practice of physicians.
Submission Type:	Initial Application
Review Type:	Delegated Review Prospective Study with participant contact (minimal risk)
Date of Approval:	September 24, 2018
Approval Expiry Date:	September 24, 2019

Dear Dr. Vincent della Zazzera,

Thank you for submitting the above referenced study. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the application and granted approval for your study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above.

The **OHSN-REB ethics approval** is applicable only for The Ottawa Hospital, University of Ottawa Heart Institute and University of Ottawa Faculty of Medicine.

An **Institutional approval (OHRI) letter is required prior to the conduct of the study** at this site. The institutional approval letter is an indication that you have satisfied ethics, contracts, departmental notifications, as applicable.

Documents Approved:

Document Name	Document Version Date
English Consent Form (version 2)	August 17, 2018
English Questionnaire (version 2)	April 19, 2018
English Recruitment Script (version 1)	August 17, 2018
French Consent Form (version 2)	August 10, 2018

French Questionnaire (version 1)	April 20, 2018
French Recruitment Script (version 1)	August 17, 2018
Protocol (version 2)	July 18, 2018

No deviations from, or changes to, the protocol should be initiated without prior written approval of an appropriate amendment from the OHSN-REB, except when necessary to eliminate immediate hazard(s) to study participants.

REB members involved in the research project do not participate in the review, discussion or decision.

If the study is to continue beyond the expiry date noted above, a Continuing Review Form must be received by the OHSN-REB on or prior to the full board submission deadline date of the meeting scheduled to occur a minimum of 30 days prior to the study expiry date. If the study has been completed by the expiry noted above, a Study Closure Report must be received by the OHSN-REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Part C, Division 5 of the Food and Drug Regulations Part 4 of the Natural Health Products Regulations Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

Ottawa Health Science Network Research Ethics Board

/kd

The Ottawa Hospital | L'Hôpital d'Ottawa
RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

September 25, 2018

Dr. Vincent della Zazzera

The Ottawa Hospital Department of Obstetrics, Gynecology, & Newborn Care Division of Maternal-Fetal Medicine

Re: OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

20180540-01H;

Recommendations for folic acid intake during pregnancy: knowledge, attitude, and practice of physicians.

Dear Dr. Vincent della Zazzera,

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact REBadministration@ohri.ca or 613-798-5555 extension 16719.

Ottawa Hospital Research Institute | Institut de recherche de l'Hôpital d'Ottawa

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9
613-798-5555 extension 16719 Fax : 613-761-4311 http://www.ohri.ca/ohsn-reb

INFORMATION AND CONSENT FORM

Title of the Study: Recommendations for folic acid intake during pregnancy: Assessing the knowledge, attitude, and practice of physicians.

Principal Investigator
Bénédicte Fontaine-Bisson, RD, PhD
Associate Professor
School of Nutrition Sciences
Faculty of Health Sciences
University of Ottawa
(613) 562-5800

Co-investigator
Vincent della Zazzera, MD, FRCSC, OBS/GYN
Clinical Researcher at l'Institut du savoir Montfort; Montfort Hospital, Staff Physician, Department of Obstetrics & Gynecology; Associate Professor, Department of OB/GYN, University of Ottawa

Co-investigator
Liana A. Mida
Master's Student
Interdisciplinary School of Health Sciences
Faculty of Health Sciences
University of Ottawa

Invitation to Participate: You are invited to participate in the abovementioned research study, a Master's project conducted by Liana Mida who is being supervised by Dr. Bénédicte Fontaine-Bisson, in collaboration with Dr. Vincent della Zazzera.
Participation: If you wish to participate in this study, please complete the attached survey. The survey should take you approximately ten (10) minutes to complete. You do not have to answer any questions that you do not want to answer. Once you have completed the survey, please return it to a member of the research team on site.

Purpose of the Study: From this research, we wish to assess physicians' knowledge, attitude, and practice regarding Canadian recommendations for women's perinatal folic acid intake.

Benefits: You may not directly benefit from your participation in this study; however, after completion of the survey questionnaire, a 20-minute seminar will be held to update you on the current state of evidence behind the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommendations and the folic acid status of Canadian women of childbearing age and those who are pregnant. During this time, light refreshments and snacks will be provided.

Confidentiality and Anonymity: You have the researcher's assurance that the information you share will remain strictly confidential and will be used solely for the purposes of this research. The only people who will have access to the research data are the research team members. Results will be published in pooled (aggregate) format. Anonymity is guaranteed since a random number will be attributed to your questionnaire and you will not be asked to provide your name; there will be no link between your survey and your personal identifying information.

Conservation of data: The data gathered from the survey will be compiled into the research database REDCap, which is housed on a completely secure server at the Montfort Hospital. The hardcopy surveys will be securely transferred to the University of Ottawa for safe storage under lock and key. Only authorized research team members will be allowed to access the database with a password using a password protected computer, and access to the hardcopy surveys.

Voluntary Participation and Withdrawal: You are under no obligation to participate and if you choose to participate, you may refuse to answer questions that you do not want to answer. Once you hand in your completed survey, the information that was collected before you withdrew will be used by the researchers as the survey is submitted anonymously. However no information will be collected after you withdraw your permission.

Information about the Study Results: The results of this study may be published in a scientific journal and presented at conferences.
If you have any questions or require more information about the study itself, you may contact the researcher or her supervisor using the phone numbers or emails mentioned herein.

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. Please contact The Ottawa Health Science Network Research Ethics Board, Chairperson at 613-798-5555 extension 16719.

Consent: Your decision to complete and return this survey will be interpreted as an indication of your consent to participate.
Please keep this form for your records. Thank you for your time and consideration.

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Titre du projet: Recommandations relatives à la consommation d'acide folique durant la grossesse : Évaluer les connaissances, les attitudes et les pratiques des médecins.

Chercheuse principale
Bénédicte Fontaine-Bisson, DtP, PhD
Professeure agrégée
École des sciences de la nutrition
Faculté des sciences de la santé
Université d'Ottawa
(613) 562-5800

Co-chercheur
Vincent della Zazzera, MD, FRCSC, OBS/GYN
Chercheur clinicien à l'Institut de savoir Montfort; Hôpital Montfort, Médecin au Département d'obstétrique et de gynécologie; Professeur agrégé, Département d'OB/GYN,
Université d'Ottawa

Co-chercheuse
Liana A. Mida
Étudiante à la maîtrise
École interdisciplinaire des sciences de la santé
Faculté des sciences de la santé
Université d'Ottawa

Invitation à participer: Vous êtes invité(e) à participer au projet de recherche de maîtrise de Liana Mida, sous la supervision de la Dre Bénédicte Fontaine-Bisson, en collaboration avec le Dr Vincent della Zazzera.

Participation: Si vous désirez participer à cette étude, veuillez compléter le sondage ci-joint. Le sondage devrait vous prendre environ dix (10) minutes à remplir. Vous n'êtes pas obligé de répondre aux questions si vous ne voulez pas y répondre. Une fois le sondage complété, veuillez le retourner à un membre de l'équipe de recherche sur place.

But de l'étude: À l'aide de ce projet de recherche, nous souhaitons évaluer les connaissances, les attitudes et les pratiques des médecins en ce qui concerne les recommandations canadiennes relatives à la consommation périnatale d'acide folique chez les femmes.

Avantages: Vous pourriez ne pas bénéficier directement de votre participation à cette étude, mais après avoir rempli le sondage, une présentation de 20 minutes vous sera donnée sur les recommandations de la Société des obstétriciens et gynécologues du Canada (SOGC) et le statut en acide folique des Canadiennes en âge de procréer et de celles qui sont enceintes. Pendant ce temps, des rafraîchissements et des collations seront servis.

Confidentialité et anonymat: Vous avez l'assurance des chercheurs que l'information que vous partagerez avec son équipe restera strictement confidentielle et sera utilisée uniquement aux fins de cette recherche. Les seules personnes qui auront accès aux données sont les membres de l'équipe de recherche. Les résultats seront publiés en format agrégé. Votre anonymat est garanti par l'utilisation d'un chiffre aléatoire qui aura été attribué à votre questionnaire. Vous n'aurez pas à fournir votre nom sur le questionnaire. Il n'y aurait donc aucun lien entre votre sondage et les informations personnelles qui pourraient vous identifier.

Conservation des données et retrait: Les informations recueillies seront compilées en ligne de manière entièrement sécurisée dans la base de données RedCap hébergée sur un serveur de l'Hôpital Montfort. Les copies papier de ce sondage seront transférées de façon sécurisée à l'Université d'Ottawa pour un rangement sécuritaire barré à clé. Seuls les membres autorisés de l'équipe de recherche pourront y accéder avec un mot de passe sur un ordinateur protégé par un mot de passe et d'avoir accès aux copies papier du sondage.

Participation volontaire et retrait: Vous n'avez aucune obligation de participer et si vous choisissez de participer, vous pouvez refuser de répondre aux questions auxquelles vous ne souhaitez pas répondre. Une fois que vous aurez remis votre sondage complété, les informations recueillies avant votre retrait à l'étude seront utilisées par les chercheurs, car le sondage est soumis anonymement. Toutefois, aucune information ne sera recueillie après que vous ayez retiré votre autorisation.

Communication des résultats: Les résultats de cette étude pourraient être publiés dans des revues scientifiques ou présentés à des congrès. Pour tout renseignement additionnel concernant cette étude, vous pouvez communiquer avec notre équipe de chercheurs par téléphone ou par courriel tel que mentionné dans ce document.

Si vous avez des questions sur les droits des participants ou les enjeux éthiques liés à cette étude, vous pouvez vous adresser à quelqu'un qui n'a aucun lien avec ce projet de recherche. Veuillez communiquer avec le président du Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa, au 613-798-5555, poste 16719.

Participation volontaire : Votre décision de compléter et remettre ce sondage sera interprétée comme une indication de votre consentement à participer. S'il vous plaît, gardez ce formulaire pour vos dossiers. Merci pour votre temps et votre considération.

INVITATION FOR PHYSICIANS TO PARTICIPATE IN A RESEARCH STUDY: Perinatal Nutrition and Health

My name is Liana Mida and I am a Master's student at the University of Ottawa. I am currently conducting my thesis research project where the overarching goal is to **assess physicians' knowledge, attitude, and practicing behaviours regarding perinatal intake of folic acid.**

I would like to invite you to participate which will involve **completing a 10-minute questionnaire.**

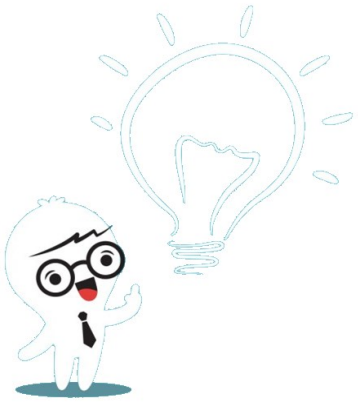
To contribute toward knowledge and education, I will email or print out informative packages to update you on the current state of evidence for perinatal folic acid intake, recommendations, and the folate status of Canadian women.

If you are interested and would like to schedule a time when I could come to the clinic or if you have any questions, please call Liana or send an email.

Thank you in advance, it is much appreciated.

Sincerely,

Liana Arielle Mida
MSc Candidate
School of Interdisciplinary Health Sciences|École interdisciplinaire des sciences de la santé
Faculty of Health Sciences|Faculté des sciences de la santé
University of Ottawa|Université d'Ottawa



Keeping up to date – to best inform all reproductive-aged patients!

INVITATION AUX MÉDECINS À PARTICIPER À UNE ÉTUDE DE RECHERCHE : Nutrition et santé périnatales

Je m'appelle Liana Mida et je suis une étudiante à la maîtrise à l'Université d'Ottawa. Je suis impliquée dans un projet de recherche qui **évalue les connaissances, les attitudes et les pratiques des médecins par rapport aux recommandations canadiennes et à l'apport périnatal des femmes enceintes en acide folique.**

Je voudrais vous inviter à participer à mon projet de recherche. Ceci implique de remplir un questionnaire d'une durée d'environ **10 minutes.**

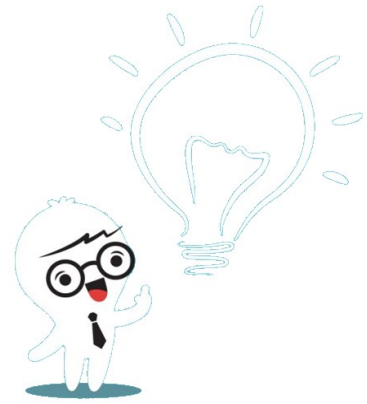
Pour contribuer à vos connaissances par l'éducation, je vais vous envoyer un courrier électronique ou imprimer une trousse d'information pour vous informer de l'état actuel des connaissances concernant la consommation périnatale d'acide folique, les recommandations et le statut en folate des femmes canadiennes.

Si vous êtes intéressé et que vous souhaitez prendre rendez-vous pour que je vienne à votre clinique ou si vous avez des questions, veuillez composer Liana ou envoyer un courrier électronique.

Merci à l'avance. Votre contribution est très appréciée.

Cordialement,

Liana Arielle Mida
MSc Candidate
School of Interdisciplinary Health Sciences|École interdisciplinaire des sciences de la santé
Faculty of Health Sciences|Faculté des sciences de la santé
University of Ottawa|Université d'Ottawa



S'informer pour mieux conseiller tous les patients en âge de procréer!

Appendix C: Hôpital Montfort REB approval documents

Montfort
Hôpital universitaire
Academic Hospital

Certificat d'approbation éthique
Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort

Le 31 octobre 2018

Chercheure principale :

Liana Arielle Mida
Université d'Ottawa

Superviseure et responsable de site Montfort

Bénédicte Fontaine-Bisson
Université d'Ottawa

Co-chercheur

Dr Vincent della Zazzera
Hôpital Montfort et Hôpital d'Ottawa

Assistante de recherche

Myriam Beaudry
Université d'Ottawa

Titre du projet : « Recommandations relatives à la consommation d'acide folique durant la grossesse : Évaluer les connaissances, les attitudes et les pratiques des médecins **»**

Numéro du dossier : 18-19-05-008

Date de début : 31 octobre 2018

Date de fin : 1er novembre 2019

En conformité avec la dernière édition de l'Énoncé de politique des trois conseils — Éthique de la recherche avec des êtres humains (ÉPTC 2), je confirme que le Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort a évalué et **approuvé votre projet de recherche** et les documents suivants pour les dates de début et de fin mentionnées ci-dessus :

- Proposition de thèse, version datée du 7 décembre 2017
- Formulaire d'information et de consentement (FR et AN) version 2, datée du 3 octobre 2018
- Questionnaire (FR et AN), version 2, datée du 3 octobre 2018
- Texte pour présenter le projet lors de la réunion des obstétriciens de Montfort (AN), soumis le 5 octobre 2018
- Invitation à la session de formation et sondage (AN), version soumise le 29 octobre 2018

Le CÉR de l'Hôpital Montfort est constitué et exerce ses activités d'une manière conforme aux Bonnes pratiques cliniques : directives consolidées, du Conseil international sur l'harmonisation des exigences techniques relatives à l'homologation des produits pharmaceutiques à usage humain (CIH-BPC E6), à la Partie C, Titre 5, du Règlement sur les aliments et drogues et aux règlements applicables, à la partie 4 du Règlement sur les produits de santé naturels; à la partie 3 du Règlement sur les instruments médicaux, au « *Code of Federal Regulations* » des États-Unis, à la Loi ontarienne de 2004 sur la protection des renseignements personnels sur la santé, de même qu'aux lois et règlements applicables en Ontario. Le CÉR de Montfort est enregistré auprès du *Department of Health and Human Services (DHHS)* et de *l'Office for Human Research Protection (OHRP)* aux États-Unis.

713 Montréal, Ottawa, ON K1K 0T2
613-746-4621
613-748-4914
www.hopitalmontfort.com

Le protocole de l'étude ne peut être modifié sans une approbation préalable du CÉR sauf s'il est question de la sécurité immédiate des participants. Le chercheur doit, avant toute utilisation, soumettre pour évaluation et approbation toutes les modifications au protocole et à la documentation destinée aux participants, par exemple, formulaire de consentement et aux outils de recrutement. Vous devez aussi aviser le CÉR immédiatement de tout événement indésirable ou nouvelle information pouvant augmenter le risque ou modifier le cours du projet de recherche.

Veuillez-nous acheminer **quatre semaines avant la date d'échéance de ce certificat d'approbation**, un rapport d'étape annuel et le cas échéant une demande de renouvellement du certificat d'approbation éthique de l'étude. Vous pouvez en tout temps soumettre un formulaire de fin d'étude et y joindre un rapport final.

Si vous avez des questions, vous pouvez communiquer avec le bureau d'éthique de la recherche (BÉR) de l'Hôpital Montfort au 613-746-4621 poste 2221 ou par courriel à ethique@montfort.on.ca.

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Hôpital Montfort

INFORMATION AND CONSENT FORM

Title of the Study: Recommendations for folic acid intake during pregnancy: Assessing the knowledge, attitude, and practice of physicians.

Principal Investigator
Bénédicte Fontaine-Bisson, RD, PhD
Associate Professor
School of Nutrition Sciences
Faculty of Health Sciences
University of Ottawa
(613) 562-5800

Co-investigator
Vincent della Zazzera, MD, FRCSC,
OBS/GYN
Clinical Researcher at l'Institut du savoir Montfort; Montfort Hospital, Staff Physician, Department of Obstetrics & Gynecology; Associate Professor, Department of OB/GYN,
University of Ottawa

Co-investigator
Liana A. Mida
Master's Student
Interdisciplinary School of Health Sciences
Faculty of Health Sciences
University of Ottawa

Invitation to Participate: You are invited to participate in the abovementioned research study, a Master's project conducted by Liana Mida who is being supervised by Professor Bénédicte Fontaine-Bisson, in collaboration with Dr. Vincent della Zazzera.

Participation: If you wish to participate in this study, please complete the attached survey. Your decision to complete and return this survey will be interpreted as an indication of your consent to participate. The survey should take you approximately ten (10) minutes to complete. You do not have to answer any questions that you do not want to answer. Once you have completed the survey, please return it to a member of the research team on site.

Purpose of the Study: From this research, we wish to assess physicians' knowledge, attitude, and practice regarding Canadian recommendations for women's perinatal folic acid intake.

Benefits: After completion of the survey questionnaire, a seminar will be held to update you on the current state of evidence behind the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommendations and the folic acid status of Canadian women of childbearing age and those who are pregnant. During this time, light refreshments and snacks will be provided.

Confidentiality and Anonymity: You have the researcher's assurance that the information you share will remain strictly confidential and will be used solely for the purposes of this research. The only people who will have access to the research data are the research team members. Results will be published in pooled (aggregate) format. Anonymity is guaranteed since a random number will be attributed to your questionnaire and you will not be asked to provide your name.

Conservation of data: The data gathered from the survey will be compiled into the research database REDCap, which is housed on a completely secure server at the Montfort Hospital. Only authorized research team members will be allowed to access the database with a password using a password protected computer. Ten years after the end of data collection, all information will be destroyed from REDCap, while the questionnaires will be shredded.

Voluntary Participation: You are under no obligation to participate and if you choose to participate, you may refuse to answer questions that you do not want to answer. Completion and return of the questionnaire by you implies consent.

Information about the Study Results: The results of this study may be published in a scientific journal and presented at conferences.

If you have any questions or require more information about the study itself, you may contact the researcher or her supervisor using the phone numbers or emails mentioned herein. If you have any questions with regards to the ethical conduct of this study, you may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5, tel.: (613) 562-5387 or ethics@uottawa.ca. Please keep this form for your records. Thank you for your time and consideration.

Signature of the principal investigator and co-investigator (MSc student)

_____	_____	_____
Bénédicte Fontaine-Bisson	Liana A. Mida	Date

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Titre du projet: Recommandations relatives à la consommation d'acide folique durant la grossesse: Évaluer les connaissances, les attitudes et les pratiques des médecins.

Chercheuse principale
Bénédicte Fontaine-Bisson, DtP, PhD
Professeure agrégée
École des sciences de la nutrition
Faculté des sciences de la santé
Université d'Ottawa
(613) 562-5800

Co-chercheur
Vincent della Zazzera, MD, FRCSC, OBS/GYN
Chercheur clinicien à l'Institut de savoir Montfort; Hôpital Montfort, Médecin au Département d'obstétrique et de gynécologie; Professeur agrégé, Département d'OB/GYN, Université d'Ottawa

Co-chercheuse
Liana A. Mida
Étudiante à la maîtrise
École interdisciplinaire des sciences de la santé
Faculté des sciences de la santé
Université d'Ottawa

Invitation à participer: Vous êtes invité(e) à participer au projet de recherche de maîtrise de Liana Mida, sous la supervision de la Professeure Bénédicte Fontaine-Bisson, en collaboration avec le Dr Vincent della Zazzera.

Participation: Si vous acceptez de participer à cette étude, vous devrez compléter le sondage ci-joint. Votre décision de remplir et de remettre ce sondage sera interprétée comme une indication de votre consentement à participer. Le sondage devrait vous prendre environ dix (10) minutes à remplir. Vous n'êtes pas obligé de répondre aux questions si vous ne voulez pas y répondre. Une fois le sondage complété, veuillez le retourner à un membre de l'équipe de recherche sur place.

But de l'étude: À l'aide de ce projet de recherche, nous souhaitons évaluer les connaissances, les attitudes et les pratiques des médecins en ce qui concerne les recommandations canadiennes relatives à la consommation périnatale d'acide folique chez les femmes.

Avantages: Après avoir rempli le sondage, un séminaire vous sera présenté concernant les recommandations de la Société des obstétriciens et gynécologues du Canada (SOGC) et le statut en acide folique des Canadiennes en âge de procréer et de celles qui sont enceintes. Pendant ce temps, des rafraîchissements et des collations seront servis.

Confidentialité et anonymat: Vous avez l'assurance des chercheurs que l'information que vous partagerez avec son équipe restera strictement confidentielle et sera utilisée uniquement aux fins de cette recherche. Les seules personnes qui auront accès aux données sont les membres de l'équipe de recherche. Les résultats seront publiés en format agrégé. Votre anonymat est garanti par l'utilisation d'un chiffre aléatoire qui aura été attribué à votre questionnaire. Vous n'aurez pas à fournir votre nom sur le questionnaire.

Conservation des données: Les informations recueillies seront compilées en ligne de manière entièrement sécurisée dans la base de données RedCap hébergée sur un serveur de l'Hôpital Montfort. Seuls les membres autorisés de l'équipe de recherche pourront y accéder avec un mot de passe sur un ordinateur protégé par un mot de passe. Enfin, dix ans après la fin de la collecte de données, les informations seront complètement effacées de la base de données RedCap, tandis que les questionnaires seront détruits à la déchiqueteuse.

Participation volontaire: Vous êtes entièrement libre de décider de participer ou non à cette étude. Si vous participez, vous pouvez refuser de répondre aux questions auxquelles vous ne souhaitez pas répondre. La complétion et la remise du questionnaire impliquent votre consentement.

Communication des résultats: Les résultats de cette étude pourraient être publiés dans des revues scientifiques ou présentés à des congrès.

Pour tout renseignement additionnel concernant cette étude, vous pouvez communiquer avec notre équipe de chercheurs par téléphone ou par courriel tel que mentionné dans de document. Pour tout renseignement sur les aspects éthiques de cette étude, vous pouvez vous adresser au Comité d'éthique de la recherche de l'Université d'Ottawa par téléphone au 613-562-5387, par courriel à ethics@uottawa.ca ou en vous présentant en personne au 550 rue Cumberland, pièce 154, Ottawa K1N 6N5. S'il vous plaît, gardez ce formulaire pour vos dossiers. Merci pour votre temps et votre considération.

Signatures de la chercheuse principale et de la co-chercheuse (étudiante à la maîtrise)

_____	_____	_____
Bénédicte Fontaine-Bisson	Liana A. Mida	Date

Appendix D: Education Package "Current State of Evidence for Perinatal Folic Acid: Recommendations, Intake and the Status of Canadian Women

Current State of Evidence for Perinatal Folic Acid: Recommendations, Intake and the Status of Canadian Women

By Liana A. Mida, MSc Candidate

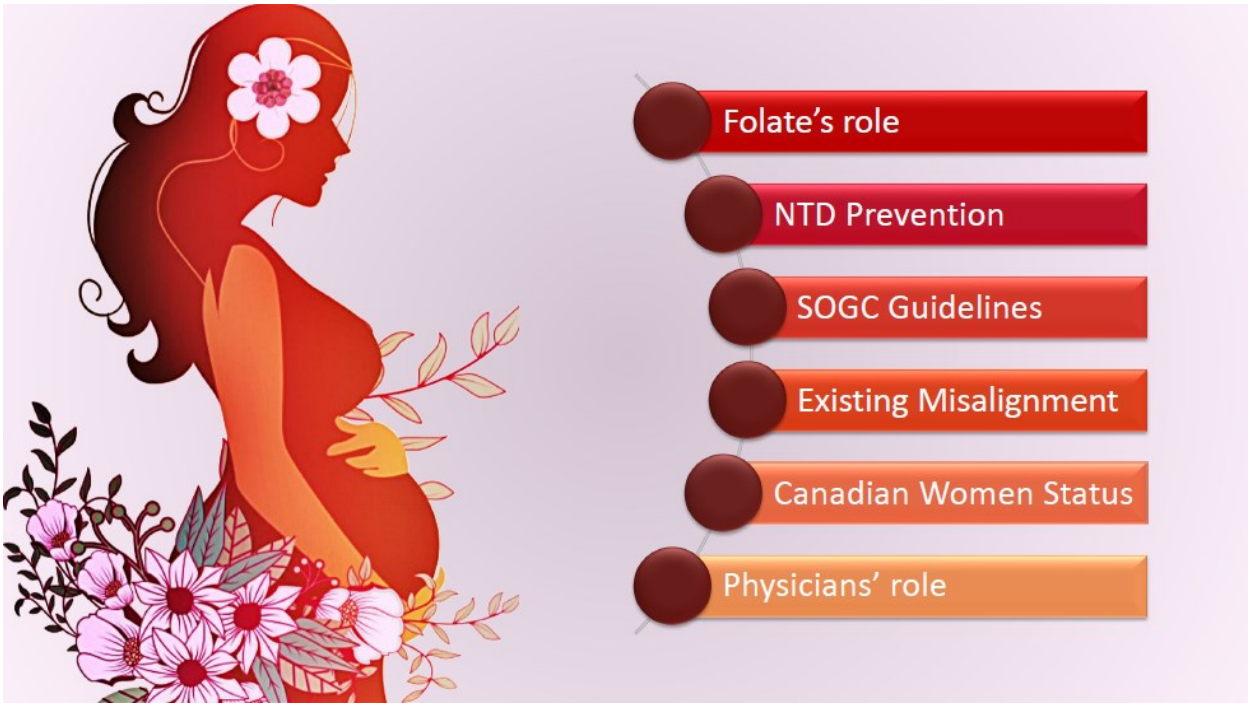
Supervisor: Dr. Bénédicte Fontaine-Bisson, RD, PhD

Co-investigator: Dr. Vincent della Zazzera, MD, FRCSC, Obs/Gyn

Interdisciplinary School of Health Sciences

Faculty of Health Sciences

uOttawa

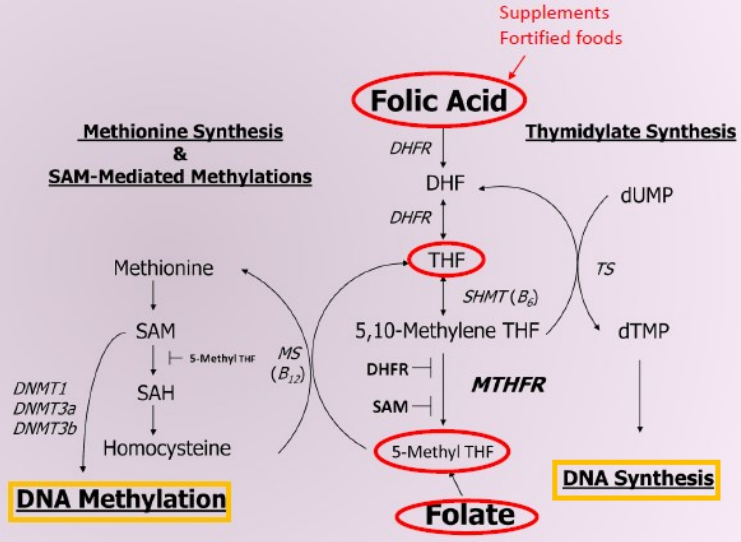


Folate Intake, Epigenetics and Fetal Programming

DNA synthesis, repair, and methylation

Cellular growth, replication, and division in fetus or placenta

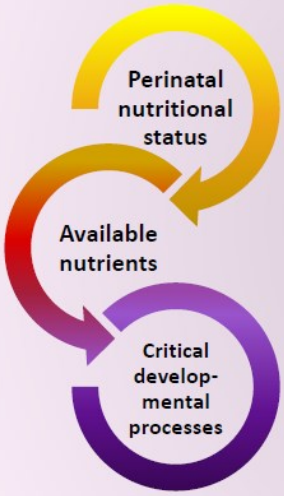
One-carbon metabolism mediated by folate cofactors



Krista S. Crider et al. (2012). *Adv Nutr*,*3*,21-38.

- Folate is a type of B vitamin that's naturally found in dietary sources and folic acid (FA) is a manmade version of it that comes from supplemental and enriched food sources.
- Folate plays a critical role in many biological processes including DNA synthesis, repair, and methylation as well as cellular growth, replication, and division. During critical periods of development such as early gestation, marginal folate intake can impair these processes in the fetus or placenta.
- It is a versatile methyl donor and cofactor mediating one-carbon metabolism which in turn are involved in epigenetic function and the abovementioned key processes.

Nutrition and Pregnancy Outcomes



- Folate deficiency is a notable cause of birth defects and developmental disabilities.
- Neural Tube Defects (NTDs) are among the most common congenital anomalies in North America.
- Other folic acid (FA)-sensitive congenital anomalies: heart defects, urinary tract anomalies, and limb defects.

- Although many birth defects and anomalies are genetically determined, it has become widely accepted that a woman's nutritional status before and during pregnancy plays an essential role in fetal programming.
- Maintaining a healthy and balanced diet, rich in essential nutrients is critical for many developmental processes such as the development of the neural tube.
- Folate deficiency is a well-recognized cause of birth defects and developmental disabilities where neural tube defects (NTDs) are among the most common congenital anomalies in North America.

Secondary Prevention of NTDs

Clinical trials: FA resulted in **70-87%** reduction of NTD recurrences.

Table 2
Results of Controlled Trials of FA Supplements for NTD Recurrence Prevention

Study	Country	*n*	NTD rate in those randomized to take FA	NTD rate in those actually taking FA	NTD rate in groups randomized to not take FA	NTD rate in groups not taking FA	Percentage reduction in risk, intent-to-treat	Percentage reduction in risk, actual FA use
Laurence et al., 1981	United Kingdom	111	3.3% (2/60)	0.0% (0/44)	7.8% (4/51)	9.0% (6/67)	58%	100%
MRC, 1991	Europe	1,195	1.0% (6/593)	0.6% (3/483)	3.5% (21/602)	3.6% (17/477)	71%	83%
Kirke et al., 1992	Ireland	364	0.0% (0/172)	NR	1.1% (1/89)	NR	100%	
ICMR, 2000	India	279	2.9% (4/137)	NR	7.0% (10/142)	NR	59%	
Pooled	All	1,949	1.2% (12/962)	0.6% (3/527)	4.1% (36/884)	4.2% (23/544)	69%	87%

NR, not reported; FA, folic acid.

Grosse and Collins. (2007). *Birth Defects Research (Part A) 79: 737-742.*

- Folic acid supplementation proved its importance and efficacy in preventing recurrent NTDs, initially.
- Grosse and Collins' meta-analysis of randomized trials of folic acid for the prevention of recurrent NTDs supported earlier findings from previous observational studies.
- The clinical trials indicated a 69% reduction in risk if analyzed on an intention-to-treat basis and an 87% reduction among women who took supplements prior to the beginning of pregnancy.

Primary Prevention of NTDs

Clinical trials (Hungarian): FA resulted in **> 90%** reduction of NTDs, proving to be an effective prevention strategy.

Intervention trials	Supplement	No supplement
Randomized controlled trial[a]		
Number of offspring	2471	2391
Expected/observed number of NTD	6.9/0	6.7/6[b]
RR (with 95% CI)	0.07 (0.04–0.13)	
Cohort-controlled trial[c]		
Number of offspring	3056	3056
Expected/observed number of NTD	8.5/1[d]	8.5/9[e]
OR (with 95% CI)	0.11 (0.01–0.91)	
Pooled data		
Number of offspring	5,527	5,447
Expected[f]/observed number of NTD	15.4/1	15.2/15
OR (with 95% CI)	0.08 (0.01–0.47)	

[a]Data from Czeizel and Dudás (1992) and Czeizel et al. (1994).

Birth Defects Research (Part A) 85:260–268 (2009)

http://www.mayoclinic.com/health/medical/IM01543

- After the success in secondary prevention, FA-supplementation was also shown to be highly effective in the *primary* prevention of NTDs.
- The findings from Czeizel and Dudas' Hungarian intervention trials indicated that periconceptional supplementation of FA prevents approximately 90% of NTDs, proving FA-supplementation to be an effective preventative strategy.
- To confer optimal protection against NTDs, it is crucial that women are informed at the appropriate time (i.e. ideally before conception) of the optimal dose and timing of supplement consumption depending on their NTD risk category.

Folic Acid Food Fortification

High incidence of unplanned pregnancies

Mandatory food fortification (1998)

46% reduction of NTD prevalence from 1993-2002

Government of Canada / Gouvernement du Canada
Canada

Recommend women of childbearing age/pregnant women to consume a daily multivitamin with 400 ug FA to prevent NTDs.

De Wals et al. (2007). *N Engl J Med, 357*(2), 135-42.

- Approximately half of pregnancies are unplanned, and even with a planned pregnancy, some women don't know they should take a supplement.
- This led the government of Canada to standardize the mandatory fortification of white flour, cornmeal, and pasta (mandatory) and cereal (optional) products in 1998.
- Post food-fortification, De Wals et al. assessed changes in the prevalence of NTDs in Canada which went from 1.58 in 1993 before fortification down to 0.86 cases for every 1000 births in 2002.

SOGC Guideline Evolution

		Folic acid dosage in mg/day			
Risk Level	Definition	1993	2003	2007	2015
Low	Women of childbearing age, male partners, low NTD risk/no NTD history, planning a pregnancy, ~~good compliance~~	0.4	0.4 – 1.0	0.4 – 1.0	0.4
Moderate	No personal NTD history, 1st and 2nd degree relative with NTD, type-1 diabetes, epilepsy treatment, folic acid antagonist use, ~~BMI>35kg/m2 , poor compliance, inconsistent birth control, possible teratogenic substance use~~, personal history of other folate-sensitive CA, maternal diabetes, teratogenic medications, maternal GI malabsorption conditions	1.0 – 4.0	4.0 – 5.0	5.0	1.0 – 4.0
High	Previous pregnancy affected by NTD (women or male partner), ~~or other potentially folate responsive congenital anomaly~~	4.0	4.0 – 5.0	5.0	4.0

- The Society of Obstetricians and Gynecologists of Canada guidelines have evolved over time. The first policy was published in 1993 and has since undergone three revisions which largely involved modifications to the definitions of the three groups.

- The dose recommended for **low-risk women** (group of interest), in addition to maintaining a healthy folate-rich diet, went from 0.4 mg/day to a range of 0.4-1.0 mg/day which has now come full circle and returned to the original dose of 0.4 mg/day.

Low-risk women

SOGC 2015 Guideline

"Daily oral multivitamin supplement containing 400 µg FA for 2-3 months before conception, throughout pregnancy, and for 4-6 weeks postpartum or as long as breast-feeding continues."

Wilson et al. (2015). *Journal of Obstetrics. 37*(6). 534-552.

- Recommendation for low-risk women from the most recent (2015) SOGC guideline titled "Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies".

- For more information, please consult the following reference:
Wilson et al. (2015). *Journal of Obstetrics, 37*(6), 534-552.

or

https://sogc.org/wp-content/uploads/2015/06/gui324CPG1505E.pdf

What's on the market?

EACH TABLET CONTAINS: / VITAMINS		CHAQUE COMPRIMÉ CONTIENT : / VITAMINES
Beta-Carotene (a source of vitamin A)	1500 mcg/µg / 2500 IU/UI	Bêtacarotène (une source de vitamine A)
Vitamin A (vitamin A acetate)	300 mcg/µg / 1000 IU/UI	Vitamine A (acétate de vitamine A)
Vitamin E (dl-α tocopheryl acetate)	13.5 mg / 30 IU/UI	Vitamine E (acétate de dl-α tocophérol)
Vitamin C (ascorbic acid)	85 mg	Vitamine C (acide ascorbique)
Folic Acid (folate)	1 mg	Acide folique (folate)
Vitamin B1 (thiamine mononitrate)	1.4 mg	Vitamine B1 (mononitrate de thiamine)
Vitamin B2 (riboflavin)	1.4 mg	Vitamine B2 (riboflavine)
Niacinamide	18 mg	Niacinamide
Vitamin B6 (pyridoxine hydrochloride)	1.9 mg	Vitamine B6 (chlorhydrate de pyridoxine)
Vitamin B12 (cyanocobalamin)	2.6 mcg/µg	Vitamine B12 (cyanocobalamine)
Vitamin D (cholecalciferol)	10 mcg/µg / 400 IU/UI	Vitamine D (cholécalciférol)
Biotin	30 mcg/µg	Biotine
Pantothenic Acid (calcium d-pantothenate)	6 mg	Acide pantothénique (d-pantothénate de calcium)
MINERALS		**MINÉRAUX**
Calcium (calcium carbonate)	250 mg	Calcium (carbonate de calcium)
Magnesium (magnesium oxide)	50 mg	Magnésium (oxyde de magnésium)
Iodine (potassium iodide)	220 mcg/µg	Iode (iodure de potassium)
Iron (ferrous fumarate)	27 mg	Fer (fumarate ferreux)
Copper (cupric sulphate)	1 mg	Cuivre (sulfate de cuivre)
Chromium (chromium chloride)	30 mcg/µg	Chrome (chlorure chromique)
Manganese (manganese sulphate)	2 mg	Manganèse (sulfate de manganèse)
Molybdenum (sodium molybdate)	50 mcg/µg	Molybdène (molybdate de sodium)
Selenium (sodium selenate)	30 mcg/µg	Sélénium (séléniate de sodium)
Zinc (zinc oxide)	7.5 mg	Zinc (oxyde de zinc)

When taken daily prior to becoming pregnant and during early pregnancy

* Lorsque pris tous les jours avant de tomber enceinte et durant les premiers stades de la grossesse

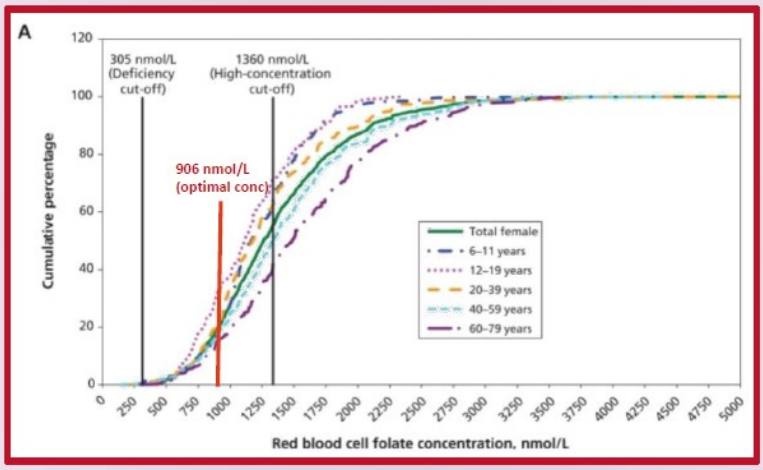
Dubois et al. (2017). *AJCN*, 106(2), 541-548.

- Most prenatal supplements contain ≥ 1,000 µg FA.
- Tolerable upper intake level (UL) = 1000 µg FA/daily.
- **A misalignment exists between prenatal supplements on market vs. expert guidelines.**

- 87.2% of Canadian women are above the UL during pregnancy.

- Despite guideline recommendations, a vast majority of prenatal supplements on the Canadian market contain an amount of folic acid equivalent to the tolerable upper intake level (UL) which is 1000 ug of folic acid a day for pregnant women.
- This has led to the currently existing misalignment between available prenatal supplements and expert guidelines. Consequently, high intake of supplemental folic acid, coupled with FA-fortified staple foods cause a large portion of women to exceed the UL throughout pregnancy.
- Left image (previous slide) is an example prenatal supplement ingredient list, containing 1 mg (1000 ug) of FA.

Canadian Status (Female)



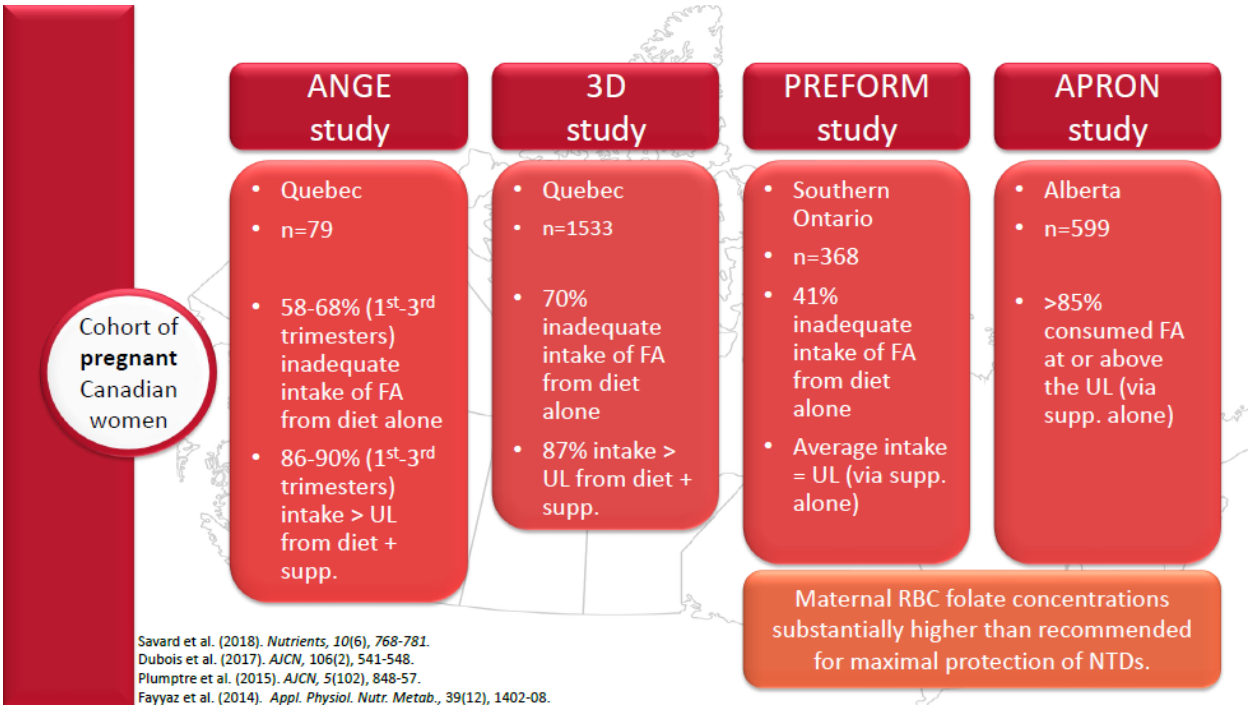
Optimal range: 906-1,000 nmol/L

No benefit >1300-1500 nmol/L

>50% are >1360 nmol/L

Colapinto et al. (2011). *CMAJ*, 183(2),E100-06.
Shi, de Groh & MacFarlane (2014). *CJPH*, 105(3), E166-71.

- Since mandatory fortification, there has been an ongoing shift in the Canadian folate status, particularly among those consuming a supplement.
- The optimal range for red blood cell (RBC) folate concentration to be maximally protected against NTDs lies between 906-1000 nmol/L, while concentrations in excess of 1300-1500 nmol/L have little to no additional benefit in the prevention of NTDs.
- [Figure] Colapinto's findings for the cumulative percentile distributions of RBC folate concentrations for the Canadian female population. Folate deficiency is virtually nonexistent whereas more than 50% of the total Canadian female population showed high folate concentrations (>1360nmol/L). Supplement consumption is undeniably important since approx. 20% showed concentrations below those considered optimal for maximal NTD protection = 906 nmol/L (indicated by red line).



Savard et al. (2018). *Nutrients, 10*(6), *768-781.*
Dubois et al. (2017). *AJCN,* 106(2), 541-548.
Plumptre et al. (2015). *AJCN, 5*(102), 848-57.
Fayyaz et al. (2014). *Appl. Physiol. Nutr. Metab.,* 39(12), 1402-08.

- Four studies regarding large Canadian cohorts of pregnant women; two studies (APRON and PREFORM) found highly elevated maternal RBC folate concentrations during each pregnancy trimester and confirmed a dramatic shift in the pregnant Canadian folate status.

- All studies concluded that in light of their findings and concerns over potential unforeseen adverse health outcomes due to epigenetic programming, the dose of folic acid in prenatal supplements should be reconsidered.

Adverse effects **potentially** associated with high FA intake

Animal Studies

Human Studies

- Inconsistent results
- Quality of evidence

Precautionary Principle

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- Evidence is lacking to confirm a potential causal relationship regarding dose-dependent adverse effects of FA; however, human studies are beginning to show outcomes comparable to those of animal studies.
- Findings suggest that excessive intake of FA induces altered phenotypes in the offspring and can lead to disease susceptibility, and thus reinforce why the supplemental dose of folic acid needs to be reconsidered.
- Given the unknown long-term effects the "precautionary principle" could be considered in clinical practice in the meantime to prevent any unintended adverse consequences.

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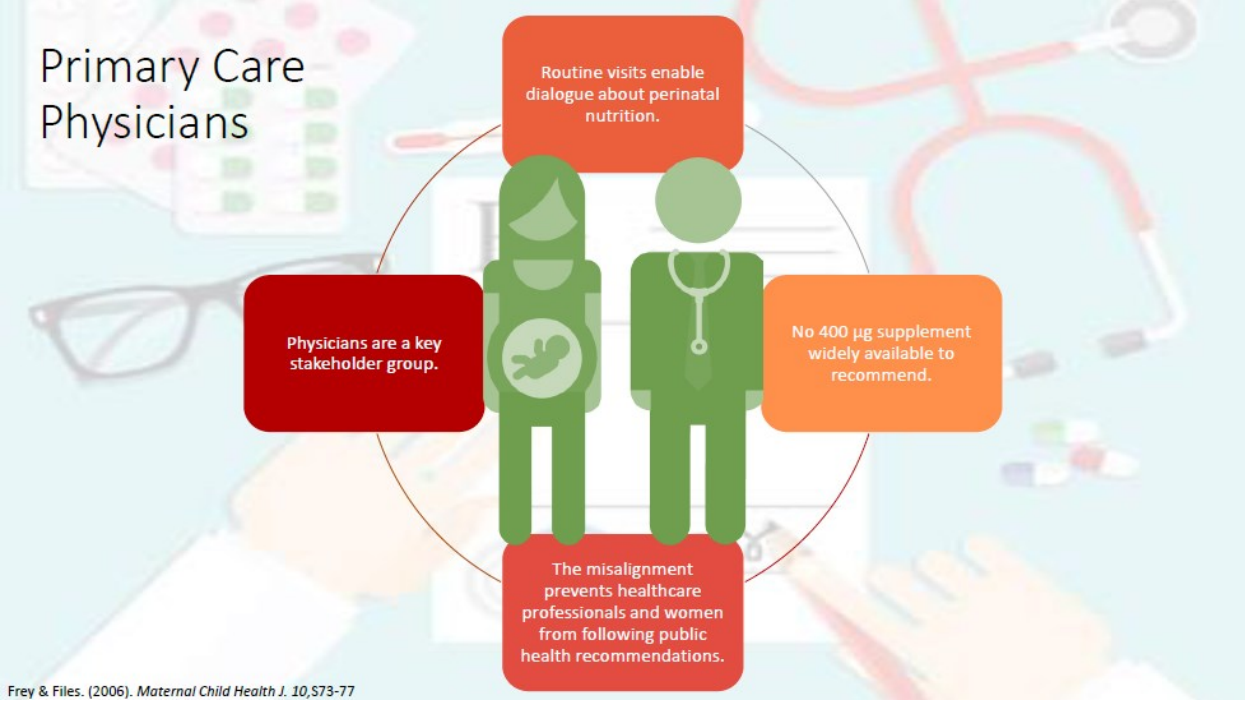
Role of Primary Care Physicians

Frey & Files. (2006). *Maternal Child Health J,* 10(1), 73-77.

- 95.3% of women prefer their physician as a source of preconception health information.
- 39% of women recall their physician discussing it with them.



- Since physicians are the linking bodies between expert guidelines and women, it's imperative that they keep up to date to best inform their patients.
- Although physicians' recommendations are highly influential, there currently does not exist a ***widely available prenatal*** supplement containing 400 ug of FA for a physician to recommend.
- Physicians have a unique positionality and are a key stakeholder group in ensuring both the health of women, their babies, and influencing the pharmaceutical industry.

Findings from a Workshop of Key Stakeholders:

"Periconceptional intake of folic acid among low-risk women: aligning prenatal supplement content with current expert guidelines"

1) Clarity and harmonization of guidelines

2) Reformulating or relabeling FA-containing supplements

3) Access to FA for all women

4) Knowledge dissemination and education of the public and HCPs

5) Attitude change

- In November 2017, a workshop held in Ottawa convened key stakeholders from academia, industry, government, and health care professional groups to discuss the misalignment.
- Five themes were developed regarding barriers and strategies in aligning prenatal supplement content with current expert guidelines.
- Physicians play a vital role in 4 out of 5, emphasizing the importance physicians play in breaking the cycle and being able to move forward with a supplement that is aligned with guidelines.

Folic Acid Resources

SOGC

- http://pregnancy.sogc.org/wp-content/uploads/2014/05/PDF_folicacid_ENG.pdf
- https://www.pregnancyinfo.ca/before-you-conceive/your-health-prior-to-pregnancy/folic-acid/

Public Health Agency of Canada

- https://www.canada.ca/en/public-health/services/pregnancy/folic-acid.html

Workshop

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6290364/

Contact info

Liana Mida, MSc Candidate
School of Interdisciplinary Health Sciences
Faculty of Health Sciences
University of Ottawa

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