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Review article

Maternal folic acid and multivitamin supplementation: International clinical evidence with considerations for the prevention of folate-sensitive birth defects

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ABSTRACT

More evidence is available for maternal intake, absorption, distribution, tissue specific concentrations, and pregnancy outcomes with folic acid (fortification/supplementation) during preconception – first trimester. This Quality Improvement prevention review used expert guidelines/opinions, systematic reviews, randomized control trials/controlled clinical trials, and observational case control/case series studies, published in English, from 1990 to August 2021. Optimization for an oral maternal folic acid supplementation is difficult because it relies on folic acid dose, type of folate supplement, bio-availability of the folate from foods, timing of supplementation initiation, maternal metabolism/genetic factors, and many other factors. There is continued use of high dose pre-food fortification 'RCT evidenced-based' folic acid supplementation for NTD recurrence pregnancy prevention. Innovation requires preconception and pregnancy use of 'carbon one nutrient' supplements (folic acid, vitamin B12, B6, choline), using the appropriate evidence, need to be considered. The consideration and adoption of directed personalized approaches for maternal complex risk could use serum folate testing for supplementation dosing choice. Routine daily folic acid dosing for low-risk women should consider a multivitamin with 0.4 mg of folic acid starting 3 months prior to conception until completion of breastfeeding. Routine folic acid dosing or preconception measurement of maternal serum folate (after 4–6 weeks of folate supplementation) could be considered for maternal complex risk group with genetic/medical/surgical co-morbidities. These new approaches for folic acid oral supplementation are required to optimize benefit (decreasing folate sensitive congenital anomalies; childhood morbidity) and minimizing potential maternal and childhood risk.

1. Background

It has been estimated that 4% to 5% of babies are born with a serious congenital anomaly and 2% to 3% (>50%) will have congenital anomalies (malformations, deformations or disruptions) that can be identified prenatally by non– invasive ultrasound screening while a further 2% will have developmental or functional conditions and minor congenital anomalies recognized at birth or during their first year of life.

For Canada, the congenital anomalies prevalence per 10,000 total births is neural tube defects 5.66 (anencephaly 1.58; spina bifida 3.53; encephalocele 0.62), congenital heart defects 20.69, oral facial cleft 16.95, and urinary tracts anomalies 11.12 (Public Health Infobase, 2021).

Two landmark RCT studies, without the benefit of folic acid food fortification, using initial experimental dosing choices from expert opinion and case-control studies, provided folic acid supplementation dosing evidence for NTD (and other major congenital anomalies) primary prevention (0.8 mg) and recurrence (4.0 mg) (MRC Vitamin Study Research Group, 1991; Czeizel and Dudás, 1992; Czeizel, 1993).

More evidence is now available regarding the maternal intake, absorption, distribution, tissue specific concentrations, and pregnancy outcomes with folic acid (FA) (fortification/supplementation) during preconception and first trimester. New clinical considerations are required using an estimated total daily intake of folic acid, with better prediction and understanding of the dietary intake (flour/corn fortification food products) and recommended supplementation dosing

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(Fig. 1) (Food Fortification Initiative, 2021).

2. Methods

This quality improvement (QI) prevention evaluation (SQUIRE2.0) is focused on the appropriate use of FA for supplementation to prevent folate sensitive birth defects (in addition to regulated food fortification). Systematic Review was not possible due to the multiple search requirements that would be necessary. **Evidence:** Published literature was retrieved through searches of PubMed, National –Society Guidelines (Society of Obstetricians and Gynecologists of Canada (SOGC), American College of Obstetrics and Gynecology (ACOG), Society of Maternal Fetal Medicine (SMFM), Royal College of Obstetrics and Gynecology (RCOG), United States Preventive Services Task Force (USPSTF)), and the Cochrane Library using appropriate controlled vocabulary/keywords (folic acid supplementation; folate food fortification; primary neural tube defect prevention; prevention of recurrence of neural tube defects; folate sensitive birth defects; folate supplementation benefit; folate supplementation risk; folate maternal physiology; maternal RBC folate level; maternal serum folate levels; folate and epilepsy; folate and obesity). Results were focused toward expert guidelines/opinions, systematic reviews, randomized control trials/controlled clinical trials, and observational case control/case series studies from 1990 to 2020 published in English. Updated literature searches were completed on a regular basis through August 2021 and were incorporated into this quality improvement review.

3. Results

3.1. Evidence: Folic acid supplementation for the prevention of folate -Sensitive birth defects

3.1.1. Pre-conception counselling

The etiologies for fetal NTD and other folate sensitive anomalies (cardiac (VSD, ASD); oral facial cleft; cleft palate; limb reduction defects; obstructive urinary tract anomalies) need to consider the 3 mechanistic pathways in preventive strategies (Wilson et al., 2021; Bibbins-Domingo et al., 2017; ACOG Practice Bulletin Neural Tube Defects, 2017; Hurst et al., 2005; Hall et al., 1988; Holmes et al., 1976; Khoury et al., 1982; Jones et al., 2013; Mulinare et al., 1988; Mills et al., 1989; Milunsky et al., 1989; Centers for Disease Control (CDC), 1983–1991; Bower and Stanley, 1989; Rothenberg et al., 2004; Cabrera et al., 2008):

Genetic factors including gene polymorphisms that affect the efficiency of folate metabolism, gene mutations, clinical effects related to DNA methylation/epigenetics, and chromosomal anomalies; at present, multifactorial risk inheritance (genetic/environmental factors) is commonly reported, but single gene and chromosomal etiologies have specific effects.

Environmental factors such as dietary folate intake (food fortification and/or dietary supplementation), gastrointestinal absorption efficiency, teratogenic medication exposure (epilepsy or folate antagonist medications), glucose metabolism (obesity, diabetes type I and II), drugs, and alcohol.

Non genetic folate receptor alpha autoantibodies (blocking; binding) have been implicated with folate related anatomical and developmental pathology.

The NTD affected population, prior to folic acid food fortification in different countries, identified the diversity of the NTD related anomalies and the co-existing anomalies (Hurst et al., 2005; Hall et al., 1988; Holmes et al., 1976; Khoury et al., 1982; Jones et al., 2013; Mulinare et al., 1988; Mills et al., 1989; Milunsky et al., 1989; Centers for Disease Control (CDC), 1983–1991; Bower and Stanley, 1989).

Table 1 summarizes the evidence supporting the oral prenatal fortification and supplementation dosing of FA for the prevention of folic acid sensitive anomalies (strong evidence (neural tube defects; cardiac (VSD/ASD); oral facial clefts; cleft palate; limb reduction defects; obstructive urinary tract anomalies) and moderate evidence (congenital hydrocephalus; transposition of the great arteries; pyloric stenosis; omphalocele) (MRC Vitamin Study Research Group, 1991;

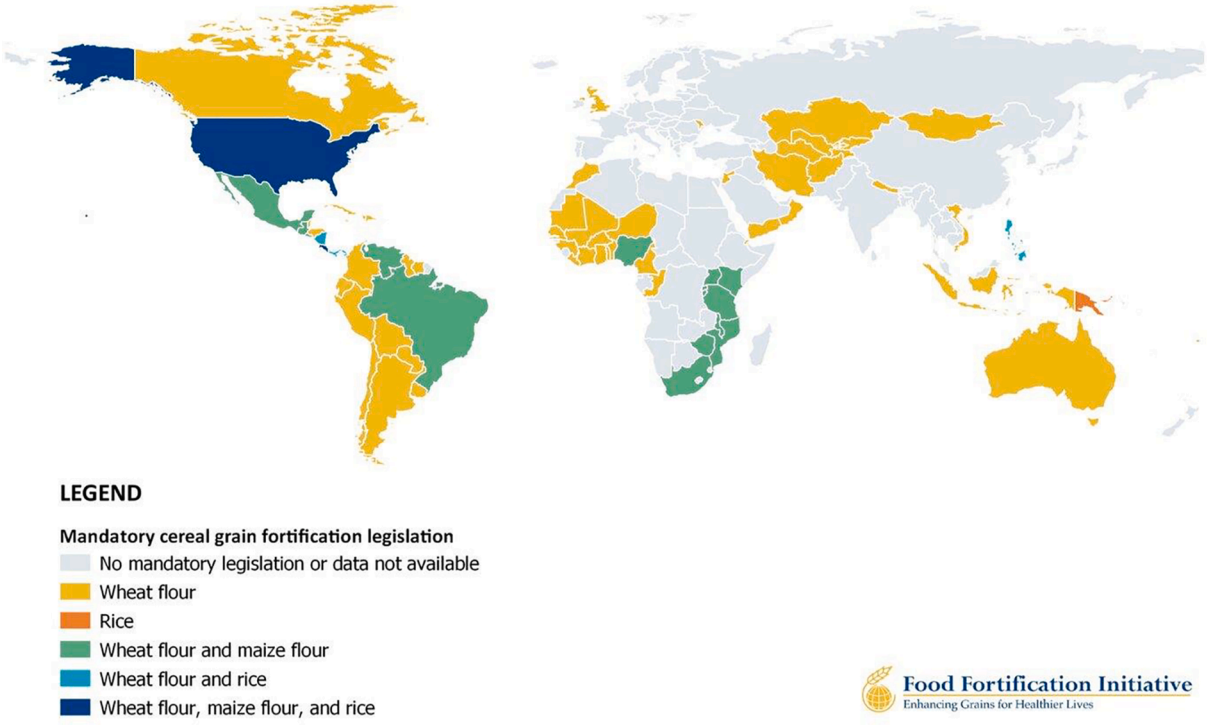

Fig. 1. Global food fortification map.

Table 1
Oral folic acid supplementation dosing evidence.

Study Design Publication Date Country Food Folic Acid Fortification Status	Study Summation	Folic acid use	NTD risk RR (95% CI)
RCT			
International multi-centered including Hungary	Medical Research Council (UK) multi-centered RCT for the prevention of NTD recurrence	Four supplementation groups:	Folic acid 4mg alone reduced NTD recurrence by 71% (0.8%, 4.3%; 0.29, 0.12-0.71)
Non-fortified 1991 (MRC Vitamin Study Research Group, 1991)		1. Folic acid 4mg 2. Other vitamins 3. Folic acid/ vitamins 4. Minerals only as control	
Hungary	RCT for primary prevention of NTD	2471 women received 0.8mg folic acid per day	Folic acid 0.8 mg supplementation:
Non-fortified		2391 women received no folic acid	0 NTDs
1992 [Czeizel and Dudás, 1992]			No folic acid: 6/2391 NTDs -0.25%
Case-control			
USA Non-fortified 1995 (Shaw et al., 1995)	Case-control study of 1007 women	Any dose < 0.4 mg 0.4-0.9 mg >1 mg	0.60 (0.46-0.79) 0.99 (0.56-1.80) 0.45 (0.31-0.72) 0.92 (0.54-1.60)
USA, Canada **Non-fortified** 1993 (Werler et al., 1993)	Case-control study 3051 women for primary prevention of NTD (0.4mg folic acid reduced primary NTD by 60%)	<0.4 mg 0.4 mg 0.5–0.9 mg > 1 mg	0.5 (0.2-1.5) 0.3 (0.1-0.6) 0.9 (0.2-4.2) 0.4 (0.1-1.3)
Other: Cohort/ Systematic Review			
USA **Fortified** 2017 (Cawley et al., 2017)	NHANES data (2007-2012) was used for modelling to determine the relation between RBC folate concentrations and NTD risk to predict NTD prevalence	400 μg/d intake of folic acid prior to pregnancy has the potential to increase the number of babies born without an NTD	Based on RBC concentrations in 4783 women, the predicted NTD prevalence was 7.3/10,000 live births (5.5-9.4); for women only consuming fortified enriched cereal grain products the NTD prevalence was 8.5/10,000 live births (6.4-10.8)
Chile, Argentina, Brazil, Canada, Costa Rica, Iran, Jordan, South Africa, USA **Fortified**	Systematic Review (1999-2009) of the prevalence of NTDs per 10,000 births pre- and post- fortification	Prevalence of NTDs related to levels of flour fortification was lowest at a folic acid level of 1.5mg/K	All 9 fortification countries showed a decrease: Canada 34-49 % Costa Rica 35-60% USA 18-28%
2012 (Castillo-Lancellotti et al., 2013)			
USA **Non-fortified** 2003 (Moore et al., 2003)	A prospective cohort study of 23,228 women with early prenatal exposures and pregnancy outcomes (pre-fortification)	1-399 DFE 400-799 DFE >800 DFE	0.29 (0.07-1.2) 0.41 (0.10-1.7) 0.56 (0.24-1.3)
USA **Non-fortified** 1998 (Bonnette et al., 1998)	Plasma homocysteine with controlled FA intake (high plasma homocysteine concentrations indicate low folate level)	Pregnant- second trimester 12 women and non-pregnant 12 women with a controlled diet of 450/850 μg/day of total folic acid food and supplement for 12 weeks	Urinary excretion of folate catabolites was similar in all women; higher rates were seen in the 850 μg/day group; plasma homocysteine was similar in both groups but lower in the pregnant group
USA **Non-fortified** 1997 (Caudill et al., 1997)	Folate status with controlled FA intake	Pregnant- second trimester 12 and non-pregnant 12 women with controlled diet of 450/850 μg/day of total folic acid food and supplement for 12 weeks	All women had RBC folate concentrations above the 906 nmol/L (mean 1453 nmol/L and 1734 nmol/L respectively

Abbreviations: DFE dietary functional equivalent; FA folic acid; NTD neural tube defect; RBC red blood cell; RCT Randomized Clinical Trial; UK United Kingdom

Czeizel and Dudás, 1992; Czeizel, 1993; Shaw et al., 1995; Werler et al., 1993; Cawley et al., 2017; Castillo-Lancellotti et al., 2013; Moore et al., 2003; Bonnette et al., 1998; Caudill et al., 1997).

Table 2 summarizes the evidenced-based studies using case–control, cohort, or RCT comparisons in populations with FA fortification/or supplementation. Folic acid combination in multivitamin supplements has been shown to reduce additional congenital anomalies. Case-control cohorts, after FA fortification, highlight the decrease in folate sensitive congenital anomaly frequencies (Czeizel, 1996; Jahanbin et al., 2018; Ingrid Goh et al., 2006; Goh and Koren, 2008; Johnson and Little, 2008; Lowry et al., 2019; Morris et al., 2018; Nishigori et al., 2019; Kondo et al., 2019; McDonnell et al., 2018; Mao et al., 2017; Liu et al., 2019; Liu et al., 2018; Liu et al., 2018; Kurdi et al., 2019; Poletta et al., 2018; Li et al., 2013; Godwin et al., 2008; Canfield et al., 2005; Canfield et al., 2009; Ray et al., 2002; Wilcox et al., 2007).

Table 3 summarizes maternal counselling issues used to identify increased risk factors for fetal NTD and for low maternal folate status (Hurst et al., 2005; Briggs et al., 2017; Greene and Copp, 2014; Han et al., 2009; Eichholzer et al., 2006; Desrosiers et al., 2018; Werler et al., 2011; Chong and Lerman, 2016; Meijer et al., 2005).

Table 4 summarizes evidenced-based drugs/medications that may interact with the physiology of maternal fortified or supplemental FA intake (Hurst et al., 2005; Briggs et al., 2017; Alpers, 2016; Stabler et al., 2009; O'Connor et al., 2016; Tsakiridis et al., 2020).

A positive impact from MMN supplementation during pregnancy for iron and folic acid is supported for several birth outcomes (decreased maternal anemia at term; reduction in low birth-weight babies; possible reduction in small-for-gestation age babies and reduced preterm birth). No important benefits or harms of MMN supplementation are found for

Table 2
Geographic NTD/congenital anomaly prevalence reported with population access to folic acid fortification and/or supplementation.

Country/Region (Time Period) Folic acid intake	**NTD**	**Other Anomalies**	**(Year)/reference**
Hungary RCT 1992 Secondary Analysis		Total anomalies MVS 20.6/1000 No MVS 40.6/1000	(1996) (Czeizel, 1996)
Meta-analysis		Significant reduction for obstructive urinary tract anomalies and cardiac VSDs	
Supplementation		FA supplementation modest reduced risk for all oral clefts (OR = 0.69; 0.60,0.78) FA alone: CL/P OR = 0.73 CP only OR = 0.75 Multivitamin with FA CL/P OR-0.65 CP only OR = 0.69	(2018) (Jahanbin et al., 2018)
Fortification	Case-control (CC) 0 0.67 (0 0.58–0 0.77)		(2006; 2008) (Ingrid Goh et al., 2006; Goh and Koren, 2008)
	Randomized Controlled Trial (RCT) 0 0.52 (0 0.39–0 0.69)	Oral facial cleft CC 0 0.63 (0 0.54–0 0.73) RCT 0 0.58 (0 0.28–1 0.19) Cardiovascular defects CC 0 0.78 (0 0.67–0 0.92) RCT 0 0.61 (0 0.40–0 0.92) Limb reduction defects CC 0 0.48 (0 0.30–0 0.76) RCT 0 0.57 (0 0.38–0 0.85) Cleft palate CC 0 0.76 (0 0.62–0 0.93) RCT 0 0.42 (0 0.06–2 0.84) Urinary tract defects CC 0 0.48 (0 0.30–0 0.76) RCT 0 0.68 (0 0.35–1 0.31) Cong hydrocephalus CC 0 0.37 (0 0.24–0 0.56) RCT 1 0.54 (0 0.53–4 0.50)	
Fortification	Case-control (CC)	Cleft lip and palate CC 0 0.75 (0 0.65–0 0.88) Cleft palate only CC 0 0.88 (0 0.76–1 0.01)	(2008) (Johnson and Little, 2008)
Geographic Populations			
Canada Alberta 2001–2015 Fortification and supplementation	Total NTD rate (2000–2014) is 0.74 per 1000 total births Total prevalence for SB was 0.37 per 1000 births with isolated SB at 0.21 per 1000 births (majority of cases were isolated (58%))	Urinary and heart defects were the most frequently identified associated anomalies Certain cases with SB are unlikely to respond to folic acid such as lipomeningomyelocele, chromosomal defects, syndromes or SB with multiple congenital anomalies.	(2018) [Lowry et al., 2019]
Europe (1980–2012) Supplementation	No decrease was detected	CHD increasing Severe CHD 1.4% Single ventricle 4.6% AVSD 3.4% ToFallot 4.1% CPAM increasing Limb reduction defects decreasing	(2018) (Morris et al., 2018)
Japan Supplementation	92,269 participants NTD 74 Spina bifida 32 Anencephaly 24 Encephalocele 19		(2019) (Nishigori et al., 2019)
Supplementation	8.29 per10,000 births 2014 8.72 per10,000 births 2015		(2019) (Kondo et al., 2019)
Ireland Supplementation	No decrease over 20 years 1.05 per 1000 pregnancies with 91% detected antenatally and 53% live born		(2018) (McDonnell et al., 2018)
China (2010–2012) Supplementation		Preconception folic acid decreased overall CHDs (OR 0.42; 0.21–0.86)	(2017) (Mao et al., 2017)
Supplementation **(2002–2011)**		Congenital limb reduction with and without FA supplementation With 2.7/10,000 Without 9.7/10,000	(2019) (Liu et al., 2019)

(*continued on next page*)

Table 2 (*continued*)

Country/Region (Time Period) Folic acid intake	**NTD**	**Other Anomalies**	**(Year)/reference**
Supplementation		Complicated Hydrocephalus 20.3/10,000 Isolated hydrocephalus 8.3/10,000 After 2009 supplementation identified decreased prevalence	(2018) (Liu et al., 2018)
Supplementation	FA supplementation reduced total NTDs for both male and female but was greater in females for total NTD and anencephaly		(2018) (Liu et al., 2018)
Saudi Arabia (single center) Supplementation	NTD 19/10,000	Anomalies total 412 per 10,000births CHD 148/10,000 Renal 113/10,000 Chrom 27/10,000	(2019) (Kurdi et al., 2019)
Latin America (1990–2013) Fortification	With FA fortification, there was a greater reduction of anencephaly and cervico-thoracis SB in females compared to males		(2018) (Poletta et al., 2018)
Single Populations			
Fortification		Heart defects CC isolated 0 0.52 (0 0.34–0 0.78) CC complex 0 0.27 (0 0.14–0 0.55)	(2013) (Li et al., 2013)
Fortification	Spina bifida Case-control (CC) 0 0.51 (0 0.36–0 0.73)	OS atrial septal defects CC 0 0.80 (0 0.69–0 0.93)	(2008) (Godwin et al., 2008)
Fortification	Anencephaly Case-control (CC)	Transposition Great Arteries	(2005) (Canfield et al., 2005)
	0 0.84 (0 0.76–0 0.94)	CC 0 0.88 (0 0.81–0 0.96) Cleft palate only	
	Spina bifida Case-control (CC) 0 0.66 (0 0.61–0 0.71)	CC 0 0.88 (0 0.82–0 0.95) Pyloric stenosis CC 0 0.95 (0 0.90–0 0.99) Omphalocele CC 0 0.79 (0 0.66–0 0.95) Upper limb reduction CC 0 0.89 (0 0.80–0 0.99)	
	Hispanic cohort (<5 years in USA) OR 3.28 (1.46–7.37)		(2009) (Canfield et al., 2009)
Fortification	Case-control (CC) Neural tube defect Pre-fortification 1.13 per 1000 pregnancies Post fortification 0.58 per 1000 pregnancies (OR 0.52 (0.40–0.67))		(2002) (Ray et al., 2002)
Supplementation	Case-control (CC)	Isolated cleft lip ± palate aOR 0.61 (0.39–0.96) High folic acid diet and supplement aOR 0.36 (0.17–0.77) Folic acid had no protection for cleft palate alone	(2007) (Wilcox et al., 2007)

Abbreviations: aOR adjusted odds ratio; CC case control; CHD congenital heart defect; CL/P cleft lip with or without cleft palate; CP cleft palate; CPAM congenital pulmonary adenomatoid malformation; FA folic acid; MVS multivitamin supplement; NTD neural tube defect; OR odds ratio; RCT randomized controlled trial; SB spina bifida; VSD ventricular septal defects.

peri-natal mortality outcomes (stillbirth, *peri*-natal and neonatal mortality) (O'Connor et al., 2016; Tsakiridis et al., 2020; Saldanha et al., 2017; Keats et al., 2019; Keats et al., 2019; Mousa et al., 2019; O'Leary and Samman, 2010; Wolf et al., 2017; Chang et al., 2013).

The 2011 *Canadian Health Measures Survey* identified that < 1% of Canadians had folate deficiency (RBC folate < 305 nmol/L), 40% had high folate concentrations (RBC folate > 1360 nmol/L) and for women of reproductive age, 22% were below the optimal NTD-risk reduction value (RBC folate < 906 nmol/L) (Colapinto et al., 2011). By 2015, a shift to higher RBC folate concentrations was identified in the population, a positive outcome for the prevention of folate sensitive birth defect but raised concern re maternal/fetal health risks. Three RBC folate concentration thresholds were used for population comparison (Colapinto et al., 2015).

Maternal evaluation, from the APrON cohort, concluded from the wide range of identified RBC folate levels that the FA supplementation counselling in this maternal cohort had not been adequate (Fayyaz et al., 2014).

3.1.1.1. One-Carbon metabolism folic acid, vitamin B12 and choline: How do they prevent?. One-carbon metabolism is responsible for purine and thymidylate synthesis and transmethylation which is critical in embryonic/fetal development. FA is a key player in one-carbon metabolism cycle (Fig. 2) (Ducker and Rabinowitz, 2017; Bailey et al., 2015; O'Leary and Samman, 2010; Ueland, 2011; Petersen et al., 2019; Brosnan et al., 2019). Table 5 summarizes one-carbon metabolism cohort studies (Petersen et al., 2019; Ray et al., 2002; Ray et al., 2007; Visentin et al., 2016; Visentin et al., 2016; Fofou-Caillierez et al., 2019; O'Malley et al., 2018; Molloy, 2018; Visentin et al., 2015; Barzilay et al., 2018; Plumptre et al., 2018; Murphy et al., 2021)

Vitamin B12 interacts as a coenzyme (O'Connor et al., 2016; Ray et al., 2002; Ray et al., 2007) while in a pregnancy cohort, 5% of women had serum vitamin B12 levels (<148 pmol/L) where recommended higher serum cut-off values (>220 pmol/L) should be considered for NTD protection (Visentin et al., 2016; Visentin et al., 2016; Farrell, 2013; Farrell et al., 2013; Colapinto et al., 2014).

Choline deficiency during pregnancy has been associated with adverse birth outcomes (impaired neurodevelopment; birth defects).

Table 3
Counselling Issues for identified increased risk factors for fetal NTD or for a low maternal folate status (Hurst et al., 2005; Briggs et al., 2017; Greene and Copp, 2014; Han et al., 2009; Eichholzer et al., 2006; Desrosiers et al., 2018; Werler et al., 2011; Chong and Lerman, 2016; Meijer et al., 2005).

Personal/Family History or Ethnic Risk	NTD: maternal or paternal affected; previous affected fetus for either parent; affected child, sibling, or second/third degree relative
Maternal Medical/Surgical co-morbidities conditions	Epilepsy: anti-epilepsy medications GI: malabsorption/inflammatory bowel disease; Crohn's disease; active Celiac disease; gastric bypass surgery; advanced liver disease Diabetes: pre-gestational diabetes (type I or II) Maternal obesity BMI > 30 kg/m2 or 80 kg (pre-pregnancy weight) Folate inhibiting medication Renal: kidney dialysis
Maternal lifestyle factors	Low Socio-economic-demographic status Immigrant women/access/language/knowledge Oral compliance factors measured by pregnancy intake of multi-vitamin Smoking Alcohol overuse Non-prescription drug use/abuse Poor or restricted (gluten-free) diet

Table 4
Interactions between drugs/medication and maternal folate concentrations (Hurst et al., 2005; Briggs et al., 2017; Alpers, 2016; Stabler et al., 2009).

Biology reduced folic acid activity	Interference with erythrocyte maturation Other	Chloramphenicol Methotrexate Metformin
Reduced folic acid levels	Impaired absorption Increased metabolism	Sulfasalazine Phenobarbital Phenytoin
Other interactions	Not well defined	Primidone Triamterene Barbiturates

The richest sources of dietary choline come from meat and egg yolk (O'Connor et al., 2016; Masih et al., 2015).

3.1.2. Management for maternal Co-Morbidity groups with identified increased risk for folate sensitive congenital anomalies

Preconception counselling for pregnancy planning is recommended for all pregnancies but will have greater preventive value with a history of genetic morbidity (includes paternal), adverse pregnancy outcomes, and maternal co-morbidity conditions (Wilson et al., 2021; Bibbins-Domingo et al., 2017; ACOG Practice Bulletin Neural Tube Defects, 2017; Wilson, 2018; ACOG Practice Bulletin Neural Tube Defects, 2019; Broughton and Douek, 2019). A three-generation pedigree for congenital anomalies (personal, fetal or neonatal) and pregnancy outcomes (live birth, stillbirth, pregnancy termination, spontaneous loss) is required for the maternal and paternal families (Table 3) World-wide NTD prevalence range is 0.3–200 per 10,000 births (Canada 5.66 per 10,000 births; USA range 3.0–6.3 per 10,000 births dependent on race and socioeconomic factors) where the identification of folate gene interactions, through transcriptome profiling studies, would allow enhanced genetic folate deficiency identification and management (Public Health Infobase, 2021; Au et al., 2017).

3.1.2.1. Genetic factor contribution to NTD. The NTD disruptive developmental processes are complex (genetic, epigenetic, metabolic, nutritional) and the identification of folate-responsive mechanisms require integrative research and collaboration (Molloy et al., 2017; Finnell et al., 2021). Neonatal folate cord blood concentration was 60% higher than maternal concentrations supporting an increased activity of one-carbon metabolism in the fetus with influence by the fetal genotype (3 fetal variants). There was no maternal folate difference between pregnancy and delivery values (Brosnan et al., 2019).

Liu et al. reported on 1517 non-chromosomal NTDs with an increasing prevalence of 3.6 (2004) to 4.6 (2015) per 10,000 total births. The NTD birth prevalence was higher in women with type 2 diabetes (rate ratio 3.74 (2.21, 6.35)), chronic illness (rate ration 3.16 (1.97, 5.07)), and history of substance abuse (rate ratio 1.88 (1.31, 2.71)) (Liu et al., 2019). These identified clinical associations support the genetic folate deficiency mechanisms and indicate primary and secondary prevention strategies are required (Liu et al., 2019; van Gool et al., 2018; Toivonen et al., 2018).

The genetic contribution for NTD malformations is further highlighted by the clinical evidence, that the siblings of the NTD proband have an increased risk for NTD (2–6%) compared with the general population risk of < 0.1% (Molloy et al., 2017). The NTD recurrence risk rate in a subsequent pregnancy is estimated at 4.0% (3.5–7.0%) but is increased to 11% in families with 2 or more NTD pregnancies/children (Chitayat et al., 2016). An early NTD embryonic-fetal losses may not always be identified but the subsequent NTD recurrence risk is present (Hartge et al., 2018).

The genetic-associated NTD risk for siblings is estimated at 20–60 X compared to the more common multifactorial-associated 2–10 X risk for other complex human diseases (type 2 diabetes, rheumatoid arthritis,

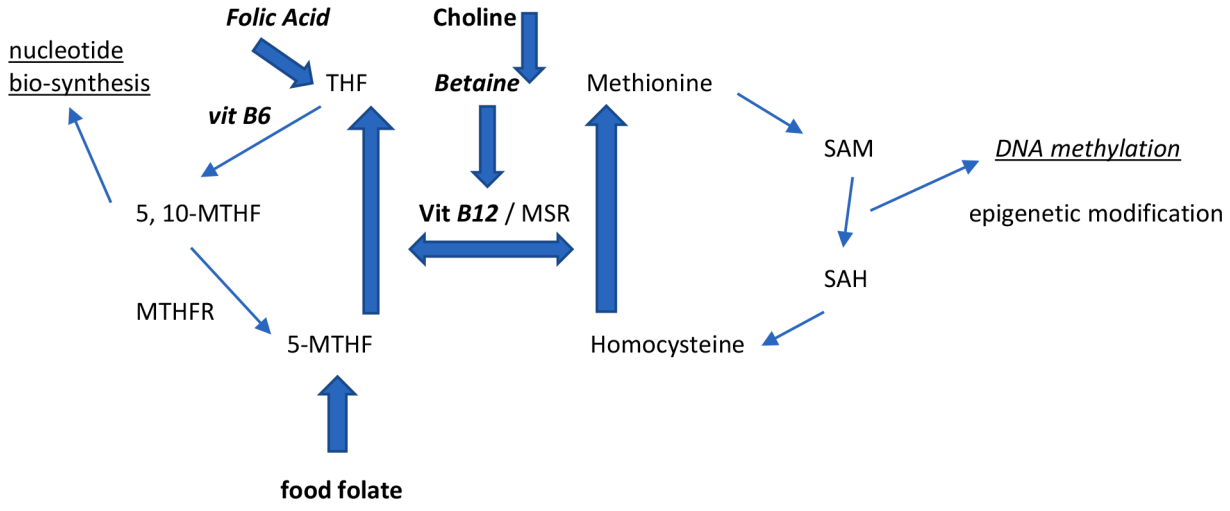

Fig. 2. Focused Diagram of the One-Carbon Metabolism Co-Factors (Ducker and Rabinowitz, 2017; Bailey et al., 2015; O'Leary and Samman, 2010; Ueland, 2011).

Table 5
One carbon co-factor clinical evaluation.

Cohort	One Carbon Element(s)	Findings	Reference
Multi-center case-control - 164 maternal NTD birth - 2831 maternal controls	folic acid B6 B12 Choline Betaine Methionine	NTD outcomes associations between oral supplementation of at least 400 μg FA and individual and concurrent (≥2) intakes of one-carbon cofactors (vitamin B6 and B12, choline, betaine, methionine) *Women with concurrent high intakes of B6, B12, choline and methionine and moderate intake of betaine had an OR 0.49 (95% CI 0.23–1.08, NS) of an NTD-affected pregnancy*	(Petersen et al., 2019)
Population-based case-control: - 89 women with fetal NTD - 422 controls	B12	Vitamin B12 use and measurement of holo-transcobalamin (vitamin B12 indicator) at 15–20 weeks gestation and *identified an increasing B12 deficiency NTD risk (aOR 2.9 (1.2–6.9)).*	(O'Connor et al., 2016; Ray et al., 2002; Ray et al., 2007)
PREFORM cohort	B12	Serum vitamin B12 measured at 12–16 weeks found levels that were deficient (17%) marginal (35%)	(Visentin et al., 2016; Visentin et al., 2016)
Selected case control: - NTD fetuses - Multiple Anomaly fetuses - Control fetuses	folic acid B12	Evaluated for serum folate and vitamin B12 concentrations and 3 liver enzymes (activity; expression, gene variants). Results identified decreased vitamin B12 concentrations in liver and cord blood and decreased expression and activity of methionine synthase in liver identifying an impaired re-methylation pathway associated with NTD risk	(Fofou-Caillierez et al., 2019)
Women with and without a child with NTD	Maternal alterations and polymorphisms in the one- carbon pathway	Significant differences between groups were found in plasma folate, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH) and SAM/SAH levels. Genotype and allele distributions of 52 SNPs in 8 genes identified 4 polymorphisms that could identify maternal NTD risk factors	(O'Malley et al., 2018)
PERFORM cohort	folic acid B12 B6 Choline	Without prenatal vitamin supplements, the dietary intake of folate and vitamin B6 would have not met requirements (dietary amounts folate 57%; vitamin B6 32%; vitamin B12 37%). Choline intake was less than adequate (<450 mg/d) in 87% of women	(Molloy, 2018)
PERFORM cohort	choline	Dietary maternal choline status, not the fetal genotype, influences cord plasma concentrations of choline metabolites	(Visentin et al., 2015)
PERFORM cohort	carbon one elements	There were no maternal differences in one-carbon nutrients/metabolites between GDM and control patients.	(Barzilay et al., 2018)
PERFORM cohort	B6	Vitamin B6 deficiency is uncommon, likely due to prevalent vitamin B6 prenatal supplement use	(Plumptre et al., 2018)
Folic Acid RCT Clinical Trial (FACT) Ancillary Study	Folic acid dose (1 or 5 mg) and One Carbon metabolism	High dose FA in early pregnancy increases serum folate but not RBC folate concentrations; high dose FA may be supraphysiologic with no evidence of altered 1-carbon metabolism	(Murphy et al., 2021)

Abbreviations: aOR adjusted odds ratio; B6 vitamin B6; B12 vitamin B12; FA folic acid; NTD neural tube defect; NS non-significant; RBC red blood cell.

schizophrenia) (Molloy et al., 2017).

SOX3 is a single exon gene located on the long arm of the X chromosome (Xq27.1). SOX3 functions as a transcription factor, that is expressed in neuroepithelial progenitor and stem cells as a key player in the regulation of embryogenesis and nervous system development. The SOX3 duplication phenotype is variable when associated with MMC in both sexes. The Xq27.1 duplication encompassing SOX3 has been implicated in the etiology of X-linked hypopituitarism associated with intellectual disability and neural tube defects. (Hureaux et al., 2019; Bauters et al., 2014; Uguen et al., 2015; Arya et al., 2019).

3.1.2.2. Maternal epilepsy. There is a strong association (drug and dosage) of anti-epileptic drugs (AEDs) with increased congenital anomalies (prevalence 2.5%) including neural tube defects. There has been no impact on the congenital anomaly prevalence with 'high dose' FA supplementation in epileptic pregnancy care (Harden, 2014; Keni et al., 2020; Baishya et al., 2020; Kashif et al., 2019; Harden et al., 2009; Harden et al., 2009; Morrow et al., 2009; Kjaer et al., 2008; Tomson et al., 2015; Herzog et al., 2017; Mahdavi et al., 2019) as the AEDs teratogenic mechanism may have no FA component or association (Harden et al., 2009; Harden et al., 2009; Morrow et al., 2009). H*igh dose FA should no longer be recommended for congenital anomaly reduction for pregnant women with epilepsy* (Stephen et al., 2019; Tomson et al., 2020; Li et al., 2021).

Benefit from FA supplementation use in epileptic pregnancy cohorts has been associated with neonatal neurodevelopmental benefits (Meador et al., 2020). A population-based biobank study (Norway) and the NEAD study (USA) have shown a decreased risk of autistic traits in children, exposed 'in utero' to AEDs, following periconceptional FA supplementation (Meador et al., 2020; Bjørk et al., 2018). Periconceptual FA supplementation in women with epilepsy is associated with better cognitive development in neonatal – childhood up to age 6 (Meador et al., 2020). The critical period for FA supplementation exposure is during the first trimester as plasma folate levels later in the pregnancy were not associated with better cognitive outcomes although they were inversely associated with autistic traits (Bjørk et al., 2018). It is recommended that fertile epileptic women using AEDs should take FA supplements continuously (Bjørk et al., 2018) with periconceptual FA supplementation, using a dose of at least 400 μg daily.

3.1.2.3. Maternal Gastro-intestinal disease. Gluten-free diet (GFD) food when compared to equivalent wheat-based food, show deficiencies in minerals (calcium, iron, magnesium, zinc) and vitamins (vitamin B 12, folate, vitamin D) (Diez-Sampedro et al., 2019; Oxentenko and Rubio-

Tapia, 2019; Makovicky et al., 2020; Hsieh et al., 2020).

Maternal lactase deficiency/polymorphism (poor gastro-intestinal nutrient absorption) is associated with NTD newborns but there were racial differences in the lactase deficiency rates (Hoang et al., 2019). Folate 'loss of function' transporter gene mutations (transporting folate from maternal intestinal lumen) may affect maternal folate availability (Findley et al., 2017).

3.1.2.4. Maternal diabetes (Pre-existing and Gestational). For pre-existing diabetes in pregnancy, the overall congenital anomaly risk is 3–4% (Broughton and Douek, 2019; Lind et al., 2019; Akbari et al., 2018; Zhao et al., 2018).

A pregestational diabetes cohort reported that daily FA supplementation (≥400 μg) was associated with a lower NTD risk (0.25 (0.04, 1.05) NS) compared to no supplementation (Petersen et al., 2019).

Although the preconception-pregnancy duration of FA supplementation and the joint effects of FA and vitamin B12 imbalance (higher folate/vitamin B12 ratio) has reported a higher pregnancy risk for the development of gestational diabetes (GDM) (Cheng et al., 2019; Huang et al., 2019; Li et al., 2019; Petersen et al., 2019). GDM may alter the concentrations of serum folate, plasma betaine and trimethylamine N-oxide (TMAO) in fetal cord blood with a possible impact on fetal epigenetic programming and later adult health (Barzilay et al., 2018).

Pre-conceptional use of inositol and FA, after one or more NTD affected pregnancies, has been evaluated in RCT and non-randomized cohorts (Greene et al., 2017; Dell'edera D, Sarlo F, Allegretti A, Epifania AA, Simone F, Lupo MG, 2017; Farren et al., 2017). Two *meta*-analyses conclude that myo-inositol supplementation has some ability to reduce the incidence of gestational diabetes (risk ratio 0.43; 95% CI (0.21–0.89)) and preterm delivery (risk ratio 0.36; 95%CI (0.17–0.73)) in pregnant women. Inositol administration during pregnancy appears to be safe and may represent a novel strategy for GDM prevention with double administration of myo-inositol 2 g per day to improve the glycemic homeostasis which may reduce GDM rate (odds ratio 0.49, 95%CI 0.24–1.03) and preterm delivery rate (odds ratio 0.35, 95%CI 0.17–0.74) (Zhang et al., 2019; Vitagliano et al., 2019).

3.1.2.5. Maternal Pre-pregnancy obesity. An obese cohort, using daily FA supplementation (at least 400 μg), was associated with a lower NTD risk (aOR 0.65(0.40,1.04) NS) compared with no supplementation (Petersen et al., 2019). In a pre-food fortification cohort, assessment of maternal pre-pregnancy weight and NTD risk reduction using ≥400 μg FA daily reduced the risk for women < 70 Kg by 40% but there was no reduction for women > 70 Kg (Kose et al., 2019).

Maternal obesity in pregnancy has an estimated prevalence of 5–10% with a significant negative impact on pregnancy outcomes.

Obese females have lower tissue folate concentrations when compared to normal weight females. There was a negative correlation between increasing BMI for both serum folate ($p = 0.03$) and plasma B12 ($p = 0.03$) but with no correlation between BMI and RBC folate concentration ($p = 0.13$) (O'Malley et al., 2018). The association of obesity and NTDs may be independent of folate intake with a clinical 'relative folate deficiency' secondary to low-grade chronic inflammation, insulin resistance, inositol, and 'dysbiotic' gut microbiome associated physiology. Maternal assessment of serum folate or RBC folate and plasma total homocysteine will assist in the management of this complex risk (Werler et al., 1996; Shaw et al., 1996; Ray et al., 2005; Zhang et al., 2021; van der Windt et al., 2021).

3.2. Social inequity issues

Social inequity factors create obstacles to timely and appropriate folic acid supplementation. The factors, leading to a lower likelihood of FA supplemental use to no supplemental use, were young maternal age, low education, low family income, multiparity, single parenthood, maternal unemployment, maternal overweight, and smoking. Immigrant and underweight woman in the cohort were more likely to receive FA supplementation but after the periconceptional period (Camier et al., 2019; Ţarcă et al., 2021).

3.2.1. Maternal folate receptor autoantibodies

The developing fetus receives folate from the mother through the placenta. It is proposed that folate as 5-MTHF, from the maternal circulation, binds to FR alpha (folate receptor alpha) present on the microvillous membrane surface of placental syncytio-trophoblast (Solanky et al., 2010). The PCFT (proton coupled folate transporter) is co-localize to this region and the receptor-mediated endocytosis of FR alpha-folate may internalize the adjacent PCFT (Solanky et al., 2010). In the endosomal compartment, acidification allows folate to be released from FR alpha and transported, coupled to a H + transporter, into the cytoplasm by PCFT (Solanky et al., 2010). Folate is exported out via RFC (reduced folate carrier) and possibly other transporters, into cytotrophoblast cells, then to the fetal vessels. While data on FA requirements and placental transport mechanisms are lacking in pregnancy and fetal development, animal studies have provided some insight into this process. Folate is actively transported across the placenta and made available to the fetus (YASUDA et al., 2008). The expression of FR alpha and FR beta in the placenta would suggest a role for both proteins in the process. In human placenta, the ratio of FR alpha and FR beta is 3:1 and in the rat, it is 1:1. While the role of FR beta in transplacental transport/fetal folate uptake is not clear, FR alpha is likely to play a major role in fetal uptake of folate since administering an antibody to FR alpha in pregnant rats causes a significant decrease in fetal uptake of folic acid. Structural development of the fetal brain requires adequate folate as evidenced by neural tube defects in the FR alpha knockout mouse (Piedrahita et al., 1999).

The presence of autoantibodies to folate receptor alpha can impair folate physiologic processes. Pregnancy associated FR autoantibodies in the pathogenesis of NTD are summarized in Table 6 (Rothenberg et al., 2004; Cabrera et al., 2008; Berrocal-Zaragoza et al., 2009; Molloy et al., 2009; Bille et al., 2010; Boyles et al., 2011; Shapira et al., 2015; Yang et al., 2016; Dong et al., 2018). The % contribution of the blocking and binding FR alpha autoantibody involvement to the overall NTD malformation prevalence is unknown. The autoantibody-NTD data has both positive and negative association studies but the dose response and genotypic variations data provides important considerations. The single case pre-pregnancy treatment report related to the reduction or elimination of the autoantibodies needs larger cohort evaluation (Yang et al., 2016).

The discovery of FR alpha autoantibodies has provided a potential mechanism by which fetal folate insufficiency could occur in the presence of normal maternal folate status. Two types of the FR alpha autoantibodies have been identified based on their functional property and epitope specificity; blocking autoantibody, which prevents binding of folate to FR alpha (by virtue of directly or sterically interfering with folate binding), and binding autoantibody, which may exert its pathology by triggering an antibody-mediated immune reaction and inflammation (Sequeira et al., 2013).

In children, these folate autoantibodies are associated with neurodevelopmental abnormalities as identified in cerebral folate deficiency syndrome, Rett syndrome and autism (ASD). Many of the parents of autistic children are also positive for these autoantibodies. Therefore, the presence of autoantibodies against FR alpha, whether transferred to the fetus from the mother during pregnancy or developed postnatally in the infant, can disrupt the transfer of folate to the brain, decreasing this essential nutrient with potential changes in the brain that may cause the ASD behavioral deficits (Ramaekers et al., 2005; Ramaekers et al., 2007; Ramaekers et al., 2007; Ramaekers et al., 2013; Frye et al., 2013).

Preconception/prenatal testing of women and men for gene mutations in folate dependent pathways and for FR alpha autoantibodies requires more study, prior to advocating for pre-pregnancy testing of

Table 6
Pregnancy reported Folate Receptor Antibodies clinical impact.

Population/ Country/Year	Study	Outcome	Reference
Pregnancy cohort/USA/ 2004	Serum from 12 pregnant women with a fetal NTD and 24 control women	9/12 women positive for autoantibodies 2/20 women positive for autoantibodies Autoantibodies blocked folic acid binding to folate receptors on placental membranes/ED27 cells/KB cells	(Rothenberg et al., 2004)
Pregnancy cohort/USA/ 2008	Serum specimens collected at 15–18 weeks with 29 pregnancies complicated by spina bifida and 76 unaffected pregnancies	OR 2.07 (CI 1.02, 4.06) anti-FBP IgM OR 2.15 (CI 1.02; 4.69) anti-FR IgG OR 3.19 (CI 1.47; 6.92) anti-FR IgM High titers of antibodies and blocking of FA binding to FR	(Cabrera et al., 2008)
Infertility/ Spain	Women planning pregnancy participated in the PREC (PRE Conception) longitudinal study of maternal nutritional status from preconception throughout pregnancy 17 cases of subfertility 25 controls	At least one positive reading for FR autoantibodies was observed in 29.4% (5/17; mean [SD] titer: 0.88 [0.39] pmol FR blocked/mL plasma) of the subfertility cases compared with in 4% (1/25; (titer: 0.19 pmol FR blocked/mL plasma) of the control group ($P < 0.05$). The risk of subfertility was 12 times higher in women with autoantibodies compared with those without (OR, 12; 95% confidence interval [CI], 1.9–129.6; $P < 0.05$).	(Berrocal-Zaragoza et al., 2009)
Variable stored blood samples/ Ireland/2009	Study 1: Analysis of stored frozen patient samples (103 NTD; 103 no fetal anomaly; 58 women never pregnant; 36 men) Study 2: evaluated frozen degradation risk	Study 1: blocking antibodies 17% of cases compared to 13% controls binding antibodies 29% of cases compared 32% controls Study 2: degradation unlikely No autoantibody association with NTD	(Molloy et al., 2009)
Nested Case Control/ Denmark/ 2010	100,419 pregnancies (1997–2003) 185 oral cleft newborns 779 controls newborns	FR alpha IgG and IgM autoantibody level was not found to be significantly different between cases and controls Blocking of folate binding to FR was similar in both groups	(Bille et al., 2010)
Nested Case Control/ Norway/ 2011	Within the Norwegian Mother and Child Cohort Study mothers of children with NTD 11	Increased binding inhibition for NTD (aOR 1.4 (CI 1.0;1.8) No increased risk for oral facial clefts and	(Boyles et al., 2011)

Table 6 (*continued*)

Population/ Country/Year	Study	Outcome	Reference
	CL± P 72 CP only 27 mothers of controls 221	CP (aOR 0.7 (CI 0.6;1.0)/(aOR 1.1 (CI 0.8;1.4)	
Pregnancy Case Report/USA/ 2015	positive for both binding and blocking autoantibodies	Successful 5th pregnancy after 4 SAs with milk-free diet, folic acid 4 mg, leucovorin 2.5 mg, , prednisone 5 mg, ASA 81 mg, vitamin D 4000 IU, vitamin B12 500ug, synthroid 25ug/progesterone 100 mg BID through 1st trimester/on this therapy her antibody titer dropped to undetectable after 300 days with natural conception	(Shapira et al., 2015)
Population-based birth defect system/ China/2016	118 mothers with NTD-affected pregnancies (fetus or neonate) 242 mothers with unaffected pregnancies (fetus or neonate)	Plasma FR autoantibodies levels IgG/IgM were significantly elevated in mothers of infants with NTDs compared with mothers of healthy controls. A dose–response relationship was found between FR autoantibodies levels and risk of NTDs ($P < 0.001$ for IgG, P 5 0.002 for IgM). The same pattern was observed in both subtypes of spina bifida and anencephaly. No significant difference in levels of cord blood FR autoantibodies was observed.	(Yang et al., 2016)
Pregnancy cohort/ China/2018	320 pregnant women to evaluate genetic polymorphisms in the folate pathway on FR autoantibodies titers	Significant associations were observed between genotypic variations and levels of FR autoantibodies. Genetic variations in MTHFR, DNMT3A, and MTHFD2 genes were associated with elevated plasma levels of FR autoantibodies.	(Dong et al., 2018)

Abbreviations: aOR adjusted odds ratio; CL/P cleft lip with or without cleft palate; CI confidence interval; CP cleft palate; FR folate receptor; NTD neural tube defect; SA spontaneous abortion.

both parents or the mother throughout pregnancy. A treatment protocol for pre-pregnancy is reported in a single case report with a larger pharmacologic treatment experience in affected children (Shapira et al., 2015; Ramaekers et al., 2008; Desai et al., 2016).

4. Evidence for oral folic acid supplementation and the maternal and Fetal-Pediatric benefit and risk

4.1. Maternal benefit/risk

Review of FA safety and documented use fully supports the benefits of mandatory FA food fortification in NTD prevention, with no established risks for adverse consequences (Field and Stover, 2018).

4.2. Maternal cancer

Evidence from *meta*-analysis reported there was no significant effect of folic acid supplementation (with a median dose of 2.0 mg/day folic acid) on the incidence of cancer of the large intestine, prostate, lung, breast, or any specific site (Vollset et al., 2013; Song et al., 2012; Castillo-Lancellotti et al., 2012; Qin et al., 2015).

Continued cancer surveillance is required as the review and the impact of folate exposure on cancer risk should continue due to conflicting study findings. A low or deficient folate status is associated with increased risks of many cancers and gene polymorphisms may impact risk in certain ethnic groups (Pieroth et al., 2018).

4.3. Adverse pregnancy events

Cochrane Review has found no conclusive evidence of benefit of FA supplementation on focused pregnancy outcomes (preterm birth, stillbirths, neonatal deaths, low birth weight babies, pre-delivery anemia, or low pre-delivery red cell folate) (Lassi et al., 2013).

4.4. Maternal serum unmetabolized folic acid (UMFA) levels during pregnancy

Concern has been raised over unmetabolized FA in the maternal circulation, due to perinatal folate fortification and supplementation. Various folate forms have been investigated in maternal and corresponding neonatal umbilical cord samples based on maternal reported perinatal FA intake with no dietary data. While unmetabolized FA identified in umbilical cord samples (50%), the concentration was 5X lower than the maternal blood while the natural folate forms showed a reverse pattern with higher cord concentrations than maternal blood samples (Obeid et al., 2010).

A secondary analysis of stored blood, from the 2006–2007 RCT Folic Acid Supplementation in the Second and Third Trimesters (FASSTT) pregnancy cohort (McNulty et al., 2013; Pentieva et al., 2016) (RCT: all women in the first trimester were given 400 μg FA per day and then they were randomized in the second and third trimester to continuing the 400 μg FA per day or a placebo) measured unmetabolized folic acid in maternal and cord blood. Plasma concentration of unmetabolized FA from supplementation and fortified FA food intake, was low or undetectable in mothers and newborns (Pentieva et al., 2016).

From a prospective study, the maternal and cord blood concentrations of folate and UMFA was determined in a cohort of pregnant women and their newborns examining the effect of maternal intake of FA and fetal genetic variants in folate metabolism on folate status. During early pregnancy, maternal plasma UMFA was detectable (≥0.2 nmol/L) in 97% of women (range: undetectable to 244 nmol/L). Plasma UMFA was detectable in 93% of cord blood samples (range: undetectable to 15 nmol/L). Cord plasma UMFA concentrations were 72% lower than maternal plasma UMFA concentrations during early pregnancy ($P < 0.0001$). The proportion of plasma UMFA that made up total serum folate was greater for maternal blood than for cord blood ($P < 0.0001$). Consistent with a previous study (Obeid et al., 2010), the lower concentration and percentage of plasma UMFA that contributed to total cord blood folate and a weak or no correlation between plasma UMFA and serum and RBC folate in cord blood, suggested that UMFA does not accumulate in the fetus even with a high folate status and detectable UMFA in mothers. Unlike adults, the fetus has limited folate storage in the liver and must use folic acid immediately available via the placenta. Therefore, the UMFA that reaches the fetus is likely metabolized to active folate forms in a more-efficient manner (Plumptre et al., 2015).

A SR for adverse maternal health outcomes associated with high serum or red blood cell folate concentrations, demonstrated no consistent relationship between increasing folate concentrations and any of the adverse health outcomes examined (Colapinto et al., 2016).

An evaluation of micronutrients, on placental function, found low maternal micronutrient status (vitamin D and A and B12, iron, folate) was associated with a range of pregnancy pathologies involving placental dysfunction (fetal growth restriction (FGR), small for gestational age (SGA), pre-eclampsia (PE), preterm birth (PTB)). The beneficial effects of micronutrients on fetal/neonatal outcomes indicates a reduction of low birth weight (LBW) (RR 0.88; 0.85–0.91) and SGA (RR 0.92, 0.86–0.98). (Baker et al., 2018).

4.5. Fetal and pediatric benefit – Risk

4.5.1. Pediatric cancer

Maternal use of prenatal multivitamins is associated with a decreased risk for pediatric tumors (OR 0.73, 95% CI 0.60 to 0.88), neuroblastoma (OR0.53, 95% CI 0.42 to 0.68), leukemia (OR 0.61, 95% CI 0.50 to 0.74), acute lymphoblastic leukemia OR 0.75 (0.66, 0.86), Wilms' tumor, primitive neuroectodermal tumors, and ependymomas (Olshan et al., 2002; Wan Ismail et al., 2019; Metayer et al., 2016; Metayer et al., 2014; Ajrouche et al., 2014; Bailey et al., 2012; Goh et al., 2007; Milne et al., 2012; Greenop et al., 2014; Amigou et al., 2012; van Uitert and Steegers-Theunissen, 2013; Linabery et al., 2012).

4.5.2. Fetal/neonatal cardiac

There is good evidence that folate supplementation may have a protective effect against severe types of CHD while the impact on CHD prevalence, could be greater than for NTD (Obeid et al., 2019; Botto et al., 1996; van Beynum et al., 2010; Shaw et al., 2009; Goldmuntz et al., 2008; Qu et al., 2020; Viswanathan et al., 2017).

4.5.3. Pediatric respiratory and allergic diseases

Childhood respiratory illnesses associated with perinatal use of folic acid, have no consistent evidence of an increased risk from FA use during the perinatal period (Crider et al., 2013; Roy et al., 2018; Trivedi et al., 2018; Vereen et al., 2019; den Dekker et al., 2018; Veeranki et al., 2015; Chen et al., 2021).

A systemic review/*meta*-analysis has suggested that pregnancy related FA intake could be a risk factor for allergic diseases especially respiratory tract allergies (RR = 1.050, 95% CI = 1.027–1.073) (Levy and Blickstein, 2006). The stratified analyses revealed the association was significant only for respiratory allergy, only for pregnant women taking oral supplements, and only for countries without FA food fortification while the *meta*-regression analysis found the risk effect decreased with increasing FA exposure. These outcome results create doubt on the conclusion of a risk association.

4.5.4. Embryonic-fetal twinning

Twinning associated with FA use in pregnancy has not been identified (Crider et al., 2013; Muggli and Halliday, 2007; Henry et al., 2018).

4.5.5. Neonatal-Childhood neurodevelopmental disorders

Studies have evaluated the fetal exposure to FA and subsequent brain development (DNA methylation; hypomethylation; imprinting; epigenetics) (Lassi et al., 2013; Obeid et al., 2010; McNulty et al., 2013). The Folic Acid Supplementation in the Second and Third Trimester (FASSTT) RCT (2005–2006) evaluated the effect of continuing FA supplementation after the first trimester of pregnancy on maternal and homocysteine responses and related effects of the newborn. The study conclusion was that continuing FA supplementation after the first trimester of

pregnancy can prevent the decline in both serum folate and red blood cell folate concentrations and increase in plasma homocysteine concentrations that otherwise occur by the later stages of pregnancy (McNulty et al., 2013).

The additional follow-up evaluations from the FASSTT RCT cohort have reported on the psychological developmental benefits for children (Caffrey et al., 2018), gene-specific DNA methylation in newborns (McNulty et al., 2019), the cognitive performance in the children (FASSTT Offspring Trial) (Caffrey et al., 2021), and the neurocognitive development in the children, eleven years after the RCT folic acid exposure (Schrott and Murphy, 2018).

The continued intake of FA in the second and third trimester of pregnancy has identified important folate-mediated epigenetic changes in genes related to brain development and function, with limited evaluations (Caffrey et al., 2019; Irwin et al., 2016; Liu et al., 2020; Liu et al., 2021). The clinical message for continued FA exposure throughout pregnancy may be most important for countries without FA food fortification (Irwin et al., 2016).

FA supplementation during early pregnancy is associated with a lower risk of offspring's autism spectrum disorders (ASD) (OR 0.57, 95% CI 0.41–0.78). The maternal daily intake of at least 400ug FA (diet and supplements) was associated with reduced ASD risk in offspring (OR 0.55, 95% CI 0.36–0.83) (Roffman, 2018).

Preconception management for timing and dosing of FA prior to conception is required (Liu et al., 2021; Roffman, 2018). Preconceptional supplements may provide the sufficient folate reserves against both, NTDs and neuropsychiatric risk (Murray et al., 2018).

While the limited human data is encouraging, the data from animal studies with excess FA intake suggest there are behavioral, morphologic, and molecular changes in the brain of offspring (Molloy and Mills, 2018).

4.6. *Folic acid supplementation dosing choice based on maternal precision monitoring directed versus evidence -based RCT directed dosing*

Table 7 (Cawley et al., 2017; Crider et al., 2018; Vatanparast et al., 2019; Teng et al., 2017; Nguyen et al., 2009; Shere et al., 2015; Higgins et al., 2000) indicates that oral FA supplementation is more efficient than food fortified diet only for congenital anomaly prevention but combining the two intake strategies increases the serum/RBC folate concentrations more quickly as folate catabolism is less effected in the first trimester. The folate catabolism is reported to peak in the third trimester, associated with the increasing fetal mass (Dolin et al., 2018).

Multiple studies for primary and recurrence NTD prevention have confirmed the utility of FA 400–800 μg dose with no studies identifying any additional NTD reduction when using FA doses > 1 mg (MRC Vitamin Study Research Group, 1991; Czeizel and Dudás, 1992; Bailey and Hausman, 2018; Rothenberg et al., 2004; Cabrera et al., 2008; Shaw et al., 1995; Werler et al., 1993; Cawley et al., 2017; Castillo-Lancellotti et al., 2013; Moore et al., 2003). Maternal FA metabolism during pregnancy suggests that FA doses > 1 mg have no increased level of maternal absorption or altered one-carbon metabolism (Murphy et al., 2021; Bailey and Hausman, 2018).

Evaluation of the maternal folate tissue status could allow for a directed or personalized supplementation dosing, optimizing for both fetal/neonatal and maternal outcomes (Chen et al., 2019) as inclusion of dietary information in folate and vitamin B12 status assessment is required and the potential use of maternal serum/RBC folate as the biomarker for risk -reduction.

Clinical laboratories are readily able to provide measurement of serum or red cell folate using automated assays where serum folate appears to offer the best combination of access, test cost and clinical information (Farrell, 2013; Farrell et al., 2013; Colapinto et al., 2014). The normal maternal serum folate range is defined as 13.5–45.3 nmol/L (the conversion factor for 1 ng/ml = 2.265 nmol/L). The plasma folate concentration threshold for NTD prevention in a population-based RCT of FA supplementation found an optimal plasma threshold of 25.5 nmol/L (with RBC folate > 906 nmol/L). The relationship between RBC and plasma folate concentrations is modified by BMI and MTHFR genotype but more significantly by low plasma vitamin B12 levels (WHO, 2020).

Table 7
Pre-conception and First Trimester Folate intake and folate sensitive birth defect protection.

Study Group and Reference	Tablet	ECGPs enriched cereal grain products	RTCs ready-to-eat cereals	Comment
Cohort [23]	FA 400ug oral			80.4% had optimal levels with a start 4–8 weeks prior to last LMP
Cohort (Higgins et al., 2000; Dolin et al., 2018)		50%	23%	obtain FA other than tablet but these sources add limited additional protection over oral use of 400ug daily
Cohort comparison (Bailey and Hausman, 2018)			18.9% with age ≥19 29–38% with age < 19	Canadian RTCs consumption but over-all the RTC group had better nutrition than non-RTC users
Cohort (Chen et al., 2019; NMH NHD EPG 15.01.pdf?ua=1 Accessed May 25, 2020) **RCT** (Tam et al., 2009)	FA 400ug oral FA 800ug oral			Optimal RBC folate level in 90% by: 16 weeks 8 weeks Steady-state was achieved more rapidly with a higher daily dose Folate steady-state is difficult to obtain due to folate catabolism but is not related to weight gain or renal clearance

Abbreviations: LMP last menstrual period; RBC red blood cell; RTC ready to eat cereal.

Hematologic defined folate deficiency was reported with a serum < 6.8 nmol/L or RBC < 226.5 nmol/L while metabolic defined folate deficiency was reported with a serum < 10 nmol/L and RBC < 340 nmol/L (Tam et al., 2009).

A 'directed screening' of maternal folate tissue status strategy could be used to identify the 'at risk' low folate status for specific complex preconception populations (van der Windt et al., 2021; Amanda and MacFarlane Deborah, 2018). *The complex 'at risk' maternal co-morbidities could include pre-gestational diabetes, epilepsy, and gastro-intestinal pathology (celiac disease, inflammatory bowel disease, gastric by-pass surgery with limited dietary requirements) and estimates the need in 20–25% of pregnant women including obesity*. Obesity, with a prevalence of 10%, has been shown to have variable outcomes for folate tissue concentrations and folate sensitive anomalies (O'Malley et al., 2018; Kose et al., 2019; Werler et al., 1996).

The directed maternal preconception folate evaluation strategy can use:

- the surrogate *'clinical serum folate equivalent'* for optimal NTD prevention is estimated at 28–30 nmol/L (RBC folate concentration > 906 nmol/L) (O'Connor et al., 2016; Chang et al., 2013; Amanda and MacFarlane Deborah, 2018)
- *clinical standard for 'sub-optimal folate'* has the serum folate concentration < 7 nmol/L (RBC folate concentration < 317 nmol/L) (Tam et al., 2009)

- vitamin B12 deficiency is considered at serum vitamin B12 level of < 150 pmol/L (Murphy et al., 2021), as holo-transcobalamin (HTC) is the functional form of B12 used by tissues, a HTC measurement can replace the standard total B12 test (Farrell, 2013)

Table 8 summarizes the routine evidenced-based FA supplementation dosing alone, if no maternal serum FA monitoring is considered in the prevention process using Table 1-2 (MRC Vitamin Study Research Group, 1991; Czeizel and Dudás, 1992; Shaw et al., 1995; Werler et al., 1993; Cawley et al., 2017; Castillo-Lancellotti et al., 2013; Moore et al., 2003; Bonnette et al., 1998; Caudill et al., 1997; Czeizel, 1996; Jahanbin et al., 2018; Ingrid Goh et al., 2006; Goh and Koren, 2008; Johnson and Little, 2008; Lowry et al., 2019; Morris et al., 2018; Nishigori et al., 2019; Kondo et al., 2019; McDonnell et al., 2018; Mao et al., 2017; Liu et al., 2019; Liu et al., 2018; Liu et al., 2018; Kurdi et al., 2019; Poletta et al., 2018; Li et al., 2013; Godwin et al., 2008; Canfield et al., 2005; Canfield et al., 2009; Ray et al., 2002; Wilcox et al., 2007). The Appendix provides additional detail for routine verses personalized FA supplementation dosing considerations.

5. Discussion

Optimization of oral maternal FA supplementation is difficult because it relies on FA dose, type of folate supplement, bio-availability of the folate from foods, timing of supplementation initiation, maternal metabolism/genetic factors, and other factors. There was continued nutrient deficiency identified with folate food fortification/dietary intake (22% of women of childbearing age had folate concentration < than the RBC folate concentration reference level of 906 nmol/L) and dietary intake vitamin B12 status showed deficiency/marginal rates of 17% and 35% during pregnancy (12–16 weeks) (O'Connor et al., 2016; Wolf et al., 2017; Visentin et al., 2016).

Although folate is mainly stored in the liver, maternal folate status can be assessed in urine, serum, plasma or the red blood cells. The measurement of folate in red blood cells (RBCs) reflects long-term folate status in the body compared to plasma/serum folate which may be influenced by recent dietary intake (Farrell, 2013).

A workshop consensus reported on considerations for periconceptional intake of FA among low-risk women in Canada. Five key challenges were identified with the need for (Amanda and MacFarlane Deborah, 2018):

1. Harmonization of guidelines, definitions and recommendations
2. More consistency for 'over the counter' and prescription FA supplement dosing related to consensus guideline recommendations
3. More optimal facilitation of access to FA-containing supplements during periconception
4. Enhanced knowledge/education transfer for patient, provider, and industry
5. Reversal of the 'more is better' attitude for vitamin and supplements

Table 8
Routine evidenced -based preconception folate and multivitamin supplementation dosing using Tables 1 and 2.

Identified folate congenital anomaly risk	Supplementation oral folate dose (mg) from preconception to 12 weeks of gestation	Oral vitamin B12 dose (ug)	Oral iron dose (mg) for routine prenatal care	Dietary intake for folate and choline rich foods	If available clinically fasting maternal folate RBC Serum (nmol/L)
Previous Neural Tube Defect history	4.0	2.6	30	yes	>907 > 28–30
History for another folate sensitive anomaly	0.8–1.0	2.6	30	yes	>907 > 28–30
Complex medical/surgical/lifestyle	0.8–1.0	2.6	30	yes	>907 > 28–30
Low	0.4	2.6	30	yes	>907 > 28–30

6. Summary

Maternal optimization for oral maternal FA supplementation is difficult because it relies on FA dose, type of folate supplement, bio-availability of the folate from foods, timing of supplementation initiation, maternal metabolism/genetic factors, and many other factors. The directed use of 'evidenced-based' folic acid supplementation in pregnancy, with or without the recommended addition of maternal serum folate (RBC folate) testing, will require further clinical evaluation and medical services/laboratory cost collaboration.

Appropriate evidence for One-Carbon metabolic supplements needs to be considered, for possible additional co-factor support for added prevention of folate-sensitive congenital anomalies (folic acid, vitamin B12, B6, choline). The preconception measurement of maternal serum folate (after 6–8 weeks of evidenced -based dose supplementation) should be considered for women with a complex risk (genetic and medical/surgical co-morbidities) for an optimized prevention of folate -sensitive birth defects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix. Detail for routine verses personalized FA supplementation dosing clinical protocol.

Maternal folic acid and multivitamin Supplementation: Best practice considerations

A consideration in the personalized/planned pregnancy Preconception Maternal Care Protocol will require directed laboratory testing access (within the first or second month of the preconception 'three-month window') and for serum folate test cost:

- for an individual with a pregnancy history of a folate -sensitive congenital anomaly outcome
- for the personalized maternal determination of the folic acid supplementation dose

All women in the reproductive age group (12–45 years) should be advised to maintain a healthy folate-rich diet as recommended including a brief periodic dietary review if considering a pregnancy due to the normal dietary variations such as vegetarian or gluten -free diets/the frequency of fortified grains-cereal intake and servings per day of fruits and vegetables/the frequency of alcohol use and the abnormal variation with GI pathology (inflammatory bowel disease/celiac disease/GI by-pass obesity surgery).

As many pregnancies are unplanned, all women who may become pregnant, need to optimize the maternal tissue folate levels for maximal protection against folate sensitive birth defects including neural tube defect. All women in the reproductive age group (12–45 years of age) who have preserved fertility should be advised about the benefits from the additional oral supplementation of folic acid and multivitamin (B6, B12), along with the consideration of the regular consumption of choline -rich foods (meat; egg yolk) and the

routine pregnancy requirement for oral iron supplementation, during female medical wellness visits (birth control renewal, Pap testing, yearly gynecology examination) whether or not a pregnancy is contemplated. Creating or updating the maternal three generation pedigree should be routinely undertaken as new medical-genetic-surgical information is frequently changing.

The overdosing of oral maternal folate supplementation has not had proven associations in childhood cohorts but animal studies have shown a potential adverse risk for neuro-developmental outcomes (behavioral; morphologic; molecular). *The use of folate supplementation at an oral 4 mg daily dose **should only** be used for women 'at risk' for recurrence of NTD malformations.*

Oral folic acid supplementation is unlikely to mask vitamin B12 deficiency (pernicious anemia). Investigations (examination or laboratory) are not generally required prior to initiating folic acid supplementation for women at a low risk of folate or vitamin B12 deficiency. Folic acid supplementation should be taken in a daily oral multivitamin which includes a 2 0.6 μg dose of vitamin B12.

LOW-RISK Primary Prevention with no maternal folate monitoring requirement/Women with a **LOW-RISK** status for a neural tube defect or other folic acid-sensitive congenital anomaly (isolated and complex cardiovascular, oral facial clefts, limb reduction defects, urinary tract defects) requires a pre-conception and first-trimester diet of folate rich foods along with the use of a daily oral multivitamin supplement that contains 400 μg (0.4 mg) folic acid, 2.6 μg vitamin B12, and iron supplement of 30 mg 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.

COMPLEX-RISK Primary Prevention with consideration for a maternal folate monitoring requirement/Women with a **COMPLEX-RISK,** for a neural tube defect or other folic acid-sensitive congenital anomaly (isolated and complex cardiovascular, oral facial clefts, limb reduction defects, urinary tract defects) , are identified by their reproductive or medical or surgical history and co-morbidity complex risk groups (**only case-control association evidence):**

a) present co-morbid medical diagnosis (pre-gestational diabetes, gastro-intestinal pathology or surgical bypass)
b) the use of medications with anti-folate physiology effects; epilepsy (phenytoin, carbamazepine, valproate); methotrexate; sulfasalazine
c) alcohol abuse
d) history of oral medication compliance issues that may impact the ability to achieve an adequate maternal folate supplementation level

Require:
Personalized

- implementation or review for pre-conception and first-trimester diet of folate rich foods
- a maternal **preconception** fasting serum folate [*'clinical serum folate equivalent' for optimal NTD prevention is estimated at 28–30 nmol/L] in the first or second month of the three months 'preconception window'* (evidenced-based protective process).
- based on the preconception serum folate level, the use of a daily oral multivitamin supplement that contains 400–1000 μg (0.4–1.0 mg) folic acid, 2.6 μg vitamin B12, and iron supplement of 30 mg for at least 2 to 3 months before conception and until 12 weeks gestation, then decrease to a daily oral multivitamin supplement with 400ug (0.4 mg) throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues.

OR
Routine

supplementation choice with no maternal serum folate testing, primary prevention has RCT evidence for supplementation with preconception use of oral folic acid 0.8–1.0 mg daily starting 3 months preconception until 12 weeks gestation to prevent fetal NTD and other folate sensitive anomalies such as isolated and complex cardiovascular, oral facial clefts, limb reduction defects, urinary tract defects, then decrease to a daily oral multivitamin supplement with 400ug (0.8 mg) throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues.

PREVIOUS FOLATE SENSITIVE BIRTH DEFECT Recurrence Prevention of Folate sensitive anomalies/Women with an increased reproductive **RISK** due to a history of a previous fetus affected with a neural tube defect or other folic acid-sensitive congenital anomaly (isolated and complex cardiovascular, oral facial clefts, limb reduction defects, urinary tract defects)

Require:

- preconception folate counselling, pregnancy planning, and implementation or review of a diet of folate rich foods, beginning at least 3 months before conception
- – the understanding that the previous RCT high dosing evidence was evaluated in

population cohorts with no folic acid food fortification programs

- availability of a preconception maternal serum folate measurement to provide a

choice for either the *personalized (maternal serum) dosing process or the RCT*

determined dosing evidence to determine the daily oral folate supplementation dose either:

a) the evidenced based RCTs with the dosing (4 mg for recurrence NTD prevention/0.8–1.0 mg for primary NTD prevention) was used in historical cohorts with no exposure to the present dietary flour folate fortification practice or maternal serum folate testing

or

b) the evidenced-based protective maternal preconception or early pregnancy fasting serum folate [*'clinical serum folate equivalent' for optimal NTD prevention is estimated at 28–30 nmol/L to determine the appropriate oral folic acid supplementation dose of 800–4000* μg *(0.8–4.0 mg)*

- pregnant women should continue their directed folate supplementation regime until 12 weeks of gestational age, from 12 weeks of gestational age, continuing through the pregnancy, and for 4 to 6 weeks post-partum or as long as breast-feeding continues, with a continued daily supplementation of an oral multivitamin containing 0.4 mg (400 μg) folic acid, 2.6 μg vitamin B12, and 30 mg iron.

OBESITY RISK Primary Prevention/Women of reproductive age **with preconception obesity (BMI > 30.0)** will require a more personal and focused folate counseling and supplementation/fetal anomalies prevention assessment (neural tube defect; cardiac; renal; oral cleft) due to their co-morbidity BMI status (class I 30.0–34.9; class II 35.0–39.9; class III > 40.0). This risk group should consider using a preconception folate tissue concentration assessment (serum folate concentration provides a good risk evaluation) and the folate supplementation management through the COMPLEX-RISK evaluation process.

The map above reflects the legislation by grain or combination of grains as follows:

- 64 countries have legislation for **wheat flour alone**
- 15 countries have legislation for **wheat flour and maize flour**

- 4 countries have legislation for **wheat flour and rice** (Nicaragua, Panama, Philippines, Solomon Islands)
- 2 countries have legislation for **wheat flour, maize flour, and rice** (Costa Rica and the United States)
- 1 country has legislation for **rice alone** (Papua New Guinea)

Citation: Food Fortification Initiative. Global Progress. Accessed 27/January/2021. http://ffinetwork.org/

One-carbon (1C) metabolism, mediated by the dietary folate, vitamin B12, vitamin B6, choline, betaine cofactors, supporting multiple physiological processes through an interlinked set of mitochondrial and cytosolic reactions (including biosynthesis (purines and thymidine), amino acid homeostasis (glycine, serine, and methionine), epigenetic maintenance, and redox defense.

(MTHFR 5, 10 methylene tetrahydrofolate reductase; MSR methionine synthetase reductase; THF tetrahydrofolate; 5-MTHF 5-methyl tetrahydrofolate; 5,10-MTHF 5,10-methylene tetrahydrofolate; SAM S-adenosyl methionine; SAH S-adenosyl homocysteine)

Vitamin B_6 is part of the vitamin B group of essential nutrients. Its active form, pyridoxal 5′-phosphate, serves as a coenzyme in some 100 enzyme reactions in amino acid, glucose, and lipid metabolism.

Vitamin B_{12} (cobalamin), is a water-soluble vitamin involved in the metabolism of every cell of the human body: it is a cofactor in DNA synthesis, and in both fatty acid and amino acid metabolism. It is particularly important in the normal functioning of the nervous system via its role in the synthesis of myelin, and in the maturation of developing red blood cells in the bone marrow.

Choline is an essential nutrient for humans and many other animals and is obtained from the diet as choline or as choline phospholipids, like phosphatidylcholine. Humans and most animals make choline de novo, but production is insufficient in humans and most species. Choline is classified as a nutrient with an amino acid-like metabolism. In most animals, choline phospholipids are necessary components in cell membranes, in the membranes of cell organelles, and in very low-density lipoproteins. Choline is required to produce acetylcholine – a neurotransmitter – and S-adenosyl methionine, a universal methyl donor involved in the synthesis of homocysteine.

Betaine orTMG (trimethylglycine) is involved in methylation reactions and detoxification of homocysteine. Betaine is similar to choline but differs in choline's terminal carboxylic acid group is reduced to a hydroxyl group. Betaine is obtained from diet as betaine or compounds containing choline in foods as whole grains, beets, and spinach. Betaine can also be synthesized in the liver and kidney. In the liver, betaine functions as a methyl donor similar to choline, folic acid, S-adenosyl methionine and vitamin B12.

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