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Review Article

Folic acid supplementation in pregnancy: established benefits, emerging evidence and public health implications

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ABSTRACT

Folic acid supplementation during pregnancy is one of the most effective nutritional interventions for preventing neural tube defects (NTDs). This narrative review synthesizes evidence from randomized controlled trials, observational studies, systematic reviews, and mechanistic research to evaluate the role of folic acid in maternal and foetal health. Robust and consistent evidence demonstrates that periconceptional folic acid supplementation substantially reduces the risk of NTDs, providing the scientific basis for global supplementation guidelines and mandatory food fortification programmes. Beyond NTD prevention, maternal folate status has been associated with a range of pregnancy and offspring outcomes, including foetal growth, neurodevelopment, and long-term metabolic health. These associations are supported by emerging evidence from epidemiological and experimental studies, with epigenetic mechanisms proposed as a key biological pathway. However, evidence for these broader effects remains less consistent and is largely observational in nature. In the post-fortification era, concerns have emerged regarding excessive folic acid intake, including the potential accumulation of unmetabolised folic acid and disruption of balanced one-carbon metabolism. This review critically evaluates established benefits, emerging evidence, and ongoing controversies surrounding folic acid supplementation in pregnancy, and identifies priorities for future research and public health practice.

Keywords: Epigenetics, Folic acid, Foetal development, Neural tube defects, Maternal nutrition

INTRODUCTION

Folic acid, the synthetic form of folate (vitamin B9), is essential for normal cellular function through its role in nucleotide synthesis, DNA repair, and methylation reactions. Among maternal micronutrients, folic acid has the strongest evidence base for preventing a specific congenital anomaly, namely neural tube defects (NTDs).[1,2] The causal relationship between inadequate maternal folate status and NTDs was firmly established through landmark randomized controlled trials conducted in the late twentieth century, which demonstrated substantial reductions in both the first occurrence and recurrence of NTDs following periconceptional folic acid supplementation.[3,4] The translation of this evidence into public health practice led to the implementation of mandatory food fortification programmes in several countries, resulting in sustained population-level reductions in NTD prevalence.[5,6] Despite these advances, NTDs remain an important global public health concern, particularly in regions without fortification or where access to preconception supplementation is limited.[7] These disparities continue to contribute significantly to perinatal mortality, long-term disability, and healthcare burden worldwide.

Folate functions within one-carbon metabolism, a network of interconnected biochemical pathways that support rapid cellular proliferation, placental development, and epigenetic regulation during early pregnancy.[8] Pregnancy is characterized by increased folate requirements, especially during early gestation when embryonic tissues are highly sensitive to disruptions in DNA synthesis and methylation capacity.[9] Inadequate folate availability

during this critical developmental window can impair normal embryogenesis, most notably affecting neural tube closure.

In recent years, research has expanded beyond NTD prevention to examine associations between maternal folate status and additional pregnancy and offspring outcomes, including foetal growth, neurodevelopment, and long-term health.[10] These associations are supported by emerging epidemiological and experimental evidence, with epigenetic mechanisms proposed as a potential biological pathway linking early nutritional exposure to later disease risk.[11] At the same time, concerns have emerged regarding excessive folic acid intake in the post-fortification era, including the presence of unmetabolised folic acid in circulation and potential disruption of balanced one-carbon metabolism.[12,13]

These developments have prompted renewed discussion regarding optimal dosing, timing, and the need to consider folic acid supplementation within the broader context of maternal nutritional status rather than as an isolated intervention.[14]

The aim of this narrative review is therefore to critically evaluate the established benefits, emerging evidence, and ongoing controversies surrounding folic acid supplementation in pregnancy, with particular emphasis on public health relevance and future research priorities.

METHODS

A structured literature search was conducted using electronic databases including PubMed, Scopus, and Web of Science. The search prioritized peer-reviewed articles from 1990 onwards, incorporating recent mechanistic and epigenetic studies through 2025. Search terms included "folic acid," "pregnancy," "neural tube defects," "one-carbon metabolism," "epigenetics," and "neurodevelopment". A narrative synthesis approach was chosen to integrate evidence from clinical trials and observational research.

FOLATE BIOCHEMISTRY AND ONE-CARBON METABOLISM

Folate plays a central biochemical role in pregnancy through its involvement in one-carbon metabolism, an integrated network of pathways responsible for nucleotide synthesis, amino acid metabolism, and methyl-group transfer reactions. These pathways are essential for cellular proliferation and differentiation during embryonic and placental development.[8] Adequate functioning of one-carbon metabolism is particularly critical during early gestation, when rapid cell division and epigenetic programming occur concurrently.

Dietary folate occurs naturally in foods such as green leafy vegetables, legumes, and fruits, whereas folic acid is the synthetic, fully oxidized form used in supplements and fortified foods. Following ingestion, folic acid must undergo enzymatic reduction before entering metabolically active folate pools. Once converted, folate derivatives participate in the folate cycle, supplying one-carbon units required for the synthesis of purines and thymidylate, thereby supporting DNA replication and repair.[8,9]

One-carbon metabolism consists of three interrelated pathways: the folate cycle, the methionine cycle, and the transsulfuration pathway. Together, these systems regulate the production of S-adenosylmethionine, the principal methyl donor for DNA, RNA, and histone methylation reactions. Disruption of these pathways can impair methylation capacity and alter gene regulation during early development, providing a mechanistic basis for the observed sensitivity of embryogenesis to maternal folate status.[8]

The methionine cycle links folate metabolism to homocysteine remethylation. Inadequate folate availability may result in elevated homocysteine concentrations, which have been associated with endothelial dysfunction and adverse pregnancy outcomes, although causal relationships remain incompletely established.[10] These metabolic interactions further highlight the importance of sufficient folate availability during pregnancy.

Folate metabolism does not function in isolation. Vitamin B_{12} is required for the remethylation of homocysteine to methionine, vitamin B_6 supports transsulfuration reactions, and choline provides an alternative source of methyl groups through betaine-dependent pathways. Imbalance among these nutrients may modify the biological effects of folic acid intake, particularly in populations exposed to high levels of synthetic folic acid through fortification and supplementation.[12,15]

Genetic variability further influences folate metabolism and individual folate requirements. Polymorphisms affecting enzymes within one-carbon metabolism, most notably methylenetetrahydrofolate reductase (MTHFR), can reduce enzymatic activity and alter folate distribution across metabolic pathways. These variants have been associated with increased susceptibility to neural tube defects, particularly in settings of low folate intake, underscoring the interaction between genetic and nutritional factors in pregnancy outcomes.[16]

PREVENTION OF NEURAL TUBE DEFECTS

NTDs, including spina bifida and anencephaly, arise from failure of neural tube closure during the first four weeks of embryonic development.[7] Among maternal nutritional factors, inadequate folate status is the most consistently and causally associated risk factor for NTDs. This relationship is supported by converging evidence from randomized controlled trials, observational studies, and population-level fortification programmes, representing

one of the strongest examples of a successful nutrition-based public health intervention.[2-6]

Evidence from randomized controlled trials

High-certainty evidence for NTD prevention originates from landmark randomized controlled trials conducted prior to the introduction of mandatory food fortification. The Medical Research Council (MRC) Vitamin Study demonstrated that high-dose folic acid supplementation (4 mg/day) in women with a previous NTD-affected pregnancy significantly reduced recurrence risk, establishing a direct causal relationship between folic acid intake and NTD prevention.[3] Similarly, the Hungarian randomised trial by Czeizel and Dudás showed that periconceptional supplementation with a folic acid-containing multivitamin significantly reduced the first occurrence of NTDs compared with trace element supplementation.[4] Together, these trials provided definitive evidence that adequate folate exposure before conception and during early pregnancy is critical for neural tube closure.

Evidence from observational studies and fortification programmes

Observational studies conducted prior to food fortification consistently supported findings from randomized trials, reporting substantial reductions in NTD risk among women using periconceptional folic acid supplements.[10] Compelling population-level evidence emerged following the implementation of mandatory folic acid fortification in several countries. In the United States and Canada, fortification programmes were associated with sustained and significant declines in NTD prevalence, confirming the effectiveness of increasing folic acid intake at the population level, particularly in the context of unplanned pregnancies.[5,6]

In the post-fortification era, additional supplementation has shown weaker associations with NTD risk, likely reflecting reduced baseline folate deficiency and challenges in accurately estimating total folate exposure. These findings do not undermine the causal role of folic acid but instead illustrate the success of fortification in lowering population-wide risk.[10]

Biological basis of neural tube defect prevention

The protective effect of folic acid against NTDs is biologically plausible and supported by extensive mechanistic evidence. Neural tube closure requires rapid cellular proliferation and tightly regulated gene expression, processes that depend on adequate nucleotide synthesis and methyl-group availability. Folate plays a central role in thymidylate and purine synthesis, which are essential for DNA replication during early embryogenesis.[8,11]

Inadequate folate availability disrupts these processes and may impair epigenetic regulation of genes involved in neural tube closure. Genetic susceptibility further modifies risk, as polymorphisms in enzymes such as methylenetetrahydrofolate reductase (MTHFR) reduce metabolic efficiency and increase vulnerability under conditions of low folate intake. Adequate periconceptional supplementation appears to mitigate this genetic risk by ensuring sufficient substrate availability.[11,16]

PREVENTION OF OTHER CONGENITAL ANOMALIES

Beyond neural tube defects, the potential role of folic acid supplementation in preventing other congenital anomalies has been widely investigated. These include congenital heart defects, orofacial clefts, and anomalies of the urinary tract and limbs. Although several observational studies suggest protective associations, the evidence for these outcomes is substantially less consistent than for neural tube defects, and causal relationships have not been definitively established.[10,14]

Congenital heart defects

Congenital heart defects (CHDs) represent one of the most common groups of congenital anomalies and contribute significantly to infant morbidity and mortality. Several large observational studies and meta-analyses have examined the association between maternal folic acid supplementation and the risk of CHDs, with some reporting modest reductions in risk among women using periconceptional supplements.[17-19]

Biological plausibility for this association is supported by the role of folate in cardiac neural crest cell migration and methylation-dependent gene regulation during early cardiogenesis. Disturbances in one-carbon metabolism and folate-related gene variants have been reported more frequently among infants with CHDs, further supporting a potential mechanistic link.[6,16,20]

However, findings remain heterogeneous across studies, with variation by CHD subtype, timing of exposure, and baseline folate status. Importantly, randomized controlled trials specifically designed to evaluate CHD prevention are lacking. Systematic reviews, therefore, conclude that while a protective association is possible, current evidence is insufficient to establish causality.[17,18]

Orofacial clefts

The relationship between maternal folic acid supplementation and orofacial clefts, including cleft lip and cleft palate, has been examined in numerous case–control and cohort studies. Several studies conducted prior to food fortification reported inverse associations between periconceptional folic acid use and risk of orofacial clefts.[21,22]

However, pooled analyses and meta-analyses have yielded inconsistent results, with some demonstrating weak

protective effects and others reporting no significant association. Differences in study design, exposure assessment, and genetic susceptibility likely contribute to this variability. Systematic reviews have therefore concluded that evidence remains inconclusive and does not support folic acid supplementation beyond existing recommendations for the specific prevention of orofacial clefts.[10,23]

Other structural anomalies

Folic acid supplementation has also been investigated in relation to anomalies of the urinary tract, limbs, and abdominal wall. Observational studies suggest that some of these defects may be partially folate-sensitive, particularly in populations with low baseline folate intake.[24,25]

Nevertheless, evidence across studies remains inconsistent, and most associations weaken after adjustment for confounding factors such as maternal socioeconomic status, overall diet quality, and concurrent micronutrient supplementation. Large systematic reviews and public health evaluations conclude that there is insufficient evidence to support a clear preventive effect of folic acid supplementation for congenital anomalies other than neural tube defects.[10,14,26]

MATERNAL HEALTH OUTCOMES

In addition to its established role in neural tube defect prevention, maternal folate status has been examined in relation to several pregnancy-related health outcomes. These include maternal anaemia, hypertensive disorders of pregnancy, and selected obstetric complications. While biological plausibility exists for several associations, evidence supporting causal effects remains limited and is derived predominantly from observational studies.[10,15]

Maternal anaemia

Folate deficiency is a recognized cause of megaloblastic anaemia, resulting from impaired DNA synthesis and abnormal erythrocyte maturation. During pregnancy, increased demands associated with expanded maternal blood volume, placental development, and foetal growth heighten the risk of deficiency when dietary intake is inadequate.[1,9]

Folic acid supplementation is effective in preventing folate-deficiency anaemia and is therefore routinely included in antenatal supplementation regimens. However, in most populations, iron deficiency remains the primary contributor to maternal anaemia.

As a result, the independent impact of folic acid supplementation on overall anaemia prevalence is difficult to isolate, particularly in settings where combined micronutrient supplementation is standard practice.[27,28]

Hypertensive disorders of pregnancy

Maternal folate status has been investigated in relation to hypertensive disorders of pregnancy, including pre-eclampsia. Proposed mechanisms include effects on homocysteine metabolism, endothelial function, and placental vascular development.[8,15]

Observational studies have reported inverse associations between folic acid supplementation and pre-eclampsia risk; however, findings are inconsistent and subject to residual confounding related to maternal health behaviours, socioeconomic status, and concurrent nutrient intake.[29,30] Evidence from randomized controlled trials specifically designed to assess hypertensive outcomes is limited, and existing data do not support folic acid supplementation as a targeted preventive strategy for pre-eclampsia.[29,31]

Other obstetric outcomes

Folic acid supplementation has also been examined in relation to outcomes such as placental abruption, preterm birth, and foetal growth restriction. Some observational studies suggest potential protective associations; however, these findings vary widely across populations and study designs.[32,33] Systematic evaluations indicate that evidence remains inconsistent and insufficient to support causal inference. Observed associations may reflect broader nutritional status or health-seeking behaviours rather than direct biological effects of folate.[10,34]

Overall, adequate folate intake is essential for maintaining maternal nutritional health, particularly for the prevention of folate-deficiency anaemia. However, current evidence does not support folic acid supplementation as a targeted intervention for the prevention of hypertensive disorders or other obstetric complications. These associations should therefore be interpreted as secondary and non-causal, reinforcing the need to avoid extending supplementation recommendations beyond established indications.

FOETAL GROWTH, NEURODEVELOPMENT AND COGNITIVE OUTCOMES

Beyond the prevention of structural neural tube defects, maternal folate status has been explored in relation to foetal growth, neurodevelopment, and later cognitive outcomes. Interest in these outcomes reflects the central role of folate in DNA synthesis, cellular proliferation, and epigenetic regulation during critical periods of development. However, compared with neural tube defect prevention, evidence for these broader outcomes is less consistent and derives largely from observational research.[8,10,11]

Foetal growth and birth outcomes

Maternal folate status has been examined in relation to foetal growth indicators, including birth weight and risk of

small-for-gestational-age birth. Several observational studies report associations between higher folate intake or circulating folate concentrations and more favourable growth outcomes.[35-37]

Biological plausibility is supported by the role of folate in placental development and cellular proliferation. Nevertheless, findings across studies are heterogeneous, and associations are sensitive to adjustment for socioeconomic factors, overall dietary quality, and concurrent micronutrient supplementation. Randomized controlled trials specifically designed to evaluate foetal growth outcomes are limited, restricting causal interpretation.[8,10,38]

Neurodevelopmental outcomes

Increasing attention has focused on potential associations between maternal folate exposure and offspring neurodevelopment beyond the prevention of structural neural tube defects. Observational cohort studies have reported associations with language development, cognition, and behavioural outcomes; however, these findings are variable and subject to residual confounding.[39-41]

Interventional evidence in this area is limited. The folic acid supplementation in the second and third trimester (FASSTT) trial represents the principal randomized study examining continued folic acid supplementation beyond early pregnancy. While this trial reported modest improvements in selected cognitive outcomes, it remains a single study with a relatively small sample size, and its findings have not yet been replicated.[15,16]

Importantly, current international guidelines continue to prioritize folic acid supplementation during the periconceptional period, reflecting the timing of neural tube closure. Evidence from later-pregnancy intervention studies, including FASSTT, has therefore not altered existing clinical recommendations.[14]

Cognitive and behavioural outcomes

Longer-term follow-up studies have explored associations between maternal folate intake and specific cognitive domains, including attention and executive function. Some studies suggest potential benefits, whereas others report null findings, contributing to an overall pattern of inconsistency.[42-44] Variability in exposure timing, baseline folate status, outcome assessment tools, and confounding by maternal education and health behaviours likely contribute to these mixed results. As such, current evidence does not permit firm conclusions regarding the causal effects of folic acid supplementation on long-term cognitive or behavioural outcomes.[10,43]

Taken together, available evidence indicates that adequate maternal folate intake is necessary for normal foetal development. However, support for additional benefits relating to neurodevelopment or long-term cognitive outcomes remains inconsistent and largely observational in nature. Current findings should therefore be regarded as hypothesis-generating rather than sufficient to inform changes to clinical or public health recommendations.

EPIGENETIC AND DEVELOPMENTAL PROGRAMMING MECHANISMS

Epigenetic mechanisms have been proposed as a biological pathway linking maternal folate status during pregnancy to long-term offspring health. Folate plays a central role in one-carbon metabolism, which supplies methyl groups required for DNA and histone methylation. These epigenetic modifications regulate gene expression without altering DNA sequence and are particularly sensitive to nutritional exposures during early development.[8,11,15]

DNA methylation and one-carbon metabolism

DNA methylation is the most extensively studied epigenetic mechanism in relation to maternal folate nutrition. Adequate folate availability supports the synthesis of S-adenosylmethionine, the universal methyl donor, thereby influencing global and gene-specific methylation patterns. Disruption of folate-dependent one-carbon metabolism may alter methylation capacity and modify gene regulation during embryogenesis.[8,11,45]

Human observational studies demonstrate associations between maternal folate status and differential DNA methylation in offspring tissues, most commonly assessed using cord blood. These methylation differences have been observed at loci involved in early development and neurobiological pathways. However, such findings represent associations rather than evidence of functional or clinical effects.[11,46]

Imprinted genes and early development

Imprinted genes, which are regulated by parent-of-origin–specific methylation marks, are established during early embryogenesis and are particularly sensitive to periconceptional nutritional exposures. Altered methylation at imprinted loci has been linked to growth regulation and developmental programming.[47]

Studies examining maternal folic acid exposure before and during pregnancy have reported associations with methylation differences at selected imprinted genes. Nonetheless, reported effect sizes are generally small, and considerable interindividual variability exists, limiting interpretation of biological significance.[18,47]

Epigenetic links to neurodevelopment

Epigenetic regulation is integral to neuronal differentiation, synaptic plasticity, and brain development. On this basis, epigenetic mechanisms have been proposed

as potential mediators of associations between maternal folate status and offspring neurodevelopment.[11,48]

Although experimental models support this biological plausibility, direct human evidence remains limited. Observed epigenetic differences have not been consistently linked to defined neurodevelopmental outcomes, and causal pathways remain speculative.[48-50]

Interaction with other methyl donors

Epigenetic regulation depends not only on folate but also on the availability of other methyl donors, including vitamin B_{12}, vitamin B_6, and choline. Imbalances within the one-carbon metabolism network may influence methylation dynamics, particularly in contexts of high folic acid intake combined with inadequate intake of complementary nutrients.[12,15,20] This integrated metabolic framework reinforces the concept that folate should not be considered in isolation, but rather as part of a broader nutritional system supporting normal developmental regulation.[8,12]

Although epigenetic research provides important mechanistic insight into how maternal folate status may influence early development, existing human evidence remains largely associative. The functional significance of observed methylation differences is uncertain, and current findings do not justify modifications to established folic acid supplementation guidelines.

RISKS AND CONTROVERSIES OF EXCESS FOLIC ACID

The success of folic acid supplementation and mandatory food fortification programmes in reducing neural tube defects has substantially improved population folate status. However, this success has also introduced new complexities in the post-fortification era, particularly in populations where folic acid intake may derive from multiple sources, including fortified foods and dietary supplements.[6,14,26]

Increasing attention has therefore focused on the possibility that both folate deficiency and excessive intake may be associated with adverse outcomes, suggesting a potential U-shaped relationship between folate exposure and health. While the benefits of preventing deficiency are well established, uncertainties remain regarding the long-term implications of sustained high intake.[12,19,51]

Excess intake and the post-fortification context

Mandatory fortification has effectively reduced folate deficiency at the population level, particularly among women with unplanned pregnancies. At the same time, concurrent use of high-dose supplements may result in total intakes exceeding physiological requirements in some individuals.[6,12,26]

Although there is no consistent evidence of acute toxicity, concerns have emerged regarding chronic exposure to high folic acid intakes, particularly in low-risk populations. These concerns have prompted calls for ongoing monitoring of total folate exposure rather than reassessment of fortification policies themselves.[13,19,52]

Unmetabolized folic acid

One frequently discussed issue relates to the presence of unmetabolised folic acid in circulation. Synthetic folic acid requires enzymatic reduction to biologically active forms, and when intake exceeds metabolic capacity, unmetabolised folic acid may appear in plasma.[12,53]

The clinical relevance of unmetabolised folic acid remains uncertain. Proposed mechanisms include interference with folate transport, altered immune responses, and masking of vitamin B_{12} deficiency. However, human evidence linking unmetabolised folic acid to adverse clinical outcomes remains limited, and current concerns are largely theoretical.[12,15,53]

Nutrient imbalance within one-carbon metabolism

Folate functions within an integrated one-carbon metabolism network that includes vitamin B_{12}, vitamin B_6, and choline. Excess folic acid intake in the context of suboptimal status of complementary nutrients may disrupt metabolic balance and methyl-group flux.[12,15,54]

This perspective highlights that potential risks associated with folic acid are unlikely to arise from folate exposure alone, but rather from imbalance within the broader nutritional system. Such considerations reinforce the importance of dietary quality and nutrient adequacy alongside supplementation.[8,15]

Interpretation and public health perspective

From a public health standpoint, it is essential to distinguish theoretical or mechanistic concerns from demonstrated clinical harm. At present, available human evidence does not support clear adverse effects of folic acid at intake levels commonly achieved through fortification and recommended supplementation.[13,14,19] Accordingly, current concerns should be interpreted as indicators for continued surveillance and research rather than as justification for changes to existing supplementation or fortification policies.[14,26,55]

Collectively, current evidence supports a balanced view in which folic acid deficiency remains a clear and preventable risk, while potential harms of excess intake remain uncertain. This emerging U-shaped framework underscores the importance of appropriate dosing, avoidance of unnecessary high-dose supplementation, and consideration of folic acid within the wider context of maternal nutritional status.[12,19,51]

CLINICAL RECOMMENDATIONS AND PUBLIC HEALTH IMPLICATIONS

Clinical and public health recommendations for folic acid supplementation are grounded in strong and consistent evidence demonstrating its effectiveness in preventing neural tube defects.

This evidence base, derived from randomized controlled trials, observational studies, and population-level fortification data, underpins current international guidance emphasizing adequate folate intake during the periconceptional period.[3-6,14]

Recommendations for low-risk populations

For women at low risk of neural tube defects, guidelines recommend daily folic acid supplementation at standard doses beginning before conception and continuing through early pregnancy. This recommendation reflects the timing of neural tube closure, which occurs during the first weeks of embryonic development, often before pregnancy is recognised.[2,14,56]

Mandatory food fortification has been implemented in several countries to improve baseline folate status and reduce inequities related to unplanned pregnancies. These programmes have contributed to sustained reductions in neural tube defect prevalence and remain a cornerstone of population-level prevention strategies.[5-7,26,57]

High-risk groups and targeted supplementation

Higher-dose folic acid supplementation is recommended for women at increased risk of neural tube defects, including those with a previous affected pregnancy or conditions associated with impaired folate metabolism. In these groups, targeted supplementation during the periconceptional period is considered appropriate due to the higher baseline risk.[3,14,16]

For other populations, routine use of high-dose supplements is not supported by current evidence. Emphasis should instead remain on appropriate dosing, preconception counselling, and avoidance of unnecessary exposure.[14,19]

Duration of supplementation

The preventive benefit of folic acid is greatest during the periconceptional period. Although continued supplementation beyond the first trimester is generally considered safe at standard doses, evidence supporting additional benefits later in pregnancy remains limited.[15,16]

As a result, current recommendations continue to prioritize early pregnancy supplementation, and findings from later-pregnancy intervention studies have not altered established clinical guidance.[14]

Balancing benefit and risk in the post-fortification era

In the post-fortification context, assessment of total folate intake from diet, fortified foods, and supplements has become increasingly important. While deficiency prevention remains the primary objective, avoidance of unnecessary high-dose supplementation in low-risk populations is also relevant.[12,19,51]

This balanced approach reflects an emerging understanding that optimal maternal health is best supported through appropriate dosing and overall nutritional adequacy rather than maximal folic acid exposure.[15,26]

Public health implications

From a public health perspective, the benefits of folic acid fortification and supplementation in preventing neural tube defects are unequivocal. Current evidence does not support modification of existing policies based on theoretical risks associated with excess intake.[14,26,57]

Ongoing surveillance of folate status and pregnancy outcomes remains important to ensure continued safety and to inform future refinements as new evidence emerges.[26,55]

FUTURE DIRECTIONS AND RESEARCH GAPS

Despite the established effectiveness of folic acid in preventing neural tube defects, important gaps remain. Evidence supporting benefits beyond early pregnancy, particularly for neurodevelopmental and long-term offspring outcomes, is limited and requires confirmation through adequately powered randomized trials with extended follow-up.

In the post-fortification era, greater attention is needed to characterize the long-term effects of sustained high folic acid exposure and to clarify potential U-shaped relationships between folate intake and health outcomes. Future research should also focus on interactions between folate and other components of one-carbon metabolism, including vitamin B_{12} and choline.

Although genetic variability in folate metabolism may influence individual responses to supplementation, current evidence does not support personalized or genotype-guided approaches in routine practice. Addressing these gaps will be essential to refining future recommendations while preserving the proven public health benefits of folic acid.

CONCLUSION

Folic acid supplementation is conclusively effective in preventing neural tube defects and remains a cornerstone of preconception and early pregnancy care. Evidence supporting benefits beyond this indication, including

effects on maternal complications, Foetal growth, and neurodevelopment, is emerging but remains inconsistent and largely observational. In the post-fortification era, attention has shifted toward balancing proven benefits with potential risks of excessive intake, emphasising appropriate dosing rather than universal high-dose supplementation. Current policies should therefore remain focused on periconceptional prevention, supported by continued surveillance and research to refine future recommendations while preserving established public health gains.

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