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EFFECTIVENESS OF FOLIC ACID FORTIFICATION AND SUPPLEMENTATION IN NEURAL TUBE DEFECTS: A CALL FOR CONTINUED EFFORTS AND FUTURE RESEARCH. A SYSTEMATIC REVIEW

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Abstract

Neural tube defects (NTDs), including spina bifida, anencephaly, and encephalocele, remain among the most common and preventable congenital anomalies worldwide. This systematic review aims to evaluate the effectiveness of folic acid fortification and supplementation in reducing the prevalence of NTDs, while also highlighting the urgent need for targeted interventions in countries such as Pakistan. A total of 37 studies were selected through a systematic literature review using databases such as PubMed, Sci-Hub, and Google Scholar. The review includes prevalence data from both global and Pakistani studies, as well as analyses of public health interventions involving folic acid. Globally, NTD prevalence remains high in many low- and middle-income countries, with studies showing reductions in NTD incidence of up to 85% with adequate folic acid intake. In Pakistan, several hospital-based studies reported a high burden of NTDs, often associated with poor maternal folic acid intake and high rates of consanguinity. Despite overwhelming global evidence supporting the efficacy of folic acid in preventing NTDs, Pakistan has yet to implement nationwide folic acid fortification. Findings from countries like Canada, the United States, and Chile demonstrate significant reductions in NTD prevalence following food fortification policies. This review concludes that mandatory folic acid fortification and enhanced peri-conceptional supplementation programs are crucial to reducing the burden of NTDs. There is a pressing need for national policies, public health education, and surveillance systems to support folic acid interventions and improve maternal and neonatal health outcomes.

INTRODUCTION

Neural tube defects are a group of common, complex congenital malformations of the central nervous system (CNS), caused by the failure of neural tube closure during embryonic development (Wang and Wang, 2023). The development of neural tube defects (NTDs) is influenced by a combination of folic acid deficiency, maternal drug exposure during pregnancy, genetic and environmental factors, and maternal fever during the first trimester. Additional risk factors include diabetes mellitus and various biochemical

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disruptions, although only one-third of all NTD cases can be attributed to a known etiology (Ocal et al., 2023).

According to the World Health Organization (WHO), millions of babies are born annually with birth defects, affecting approximately 6% of all newborns. Among these, NTDs are one of the most frequent and are currently the second most common major birth defect after cardiovascular anomalies (Tirsit et al., 2023; Koren and Kaplan, 2021). NTDs can result in lifelong disability, disfigurement, malnutrition, and a significant disease burden, with an estimated 26.06 million disability-adjusted life years (DALYs) attributable to NTDs (Mukherjee, 2023). Globally, around 300,000 cases occur annually, leading to approximately 88,000 deaths (Wald, 2022).

NTDs result from defective midline fusion of the neural tube, leading to cranial or spinal dysraphism. These may involve nerve roots, the spinal cord, or vertebrae and are categorized as open or closed defects (Sen and Jangra, 2023). Open NTDs include craniorachiasis, anencephaly, and myelomeningocele, while closed forms encompass encephalocele, meningocele, and spina bifida occulta (CoppStanier and Greene, 2013; McComb, 2015; Avagliano et al., 2019). In open NTDs, malformation of vertebrae or the skull exposes neural tissue to amniotic fluid, leading to degradation, whereas closed defects involve membranes, fat, or bone abnormalities (Isaković et al., 2022).

Spina bifida and anencephaly are the most prevalent types of NTDs, with 1,400 and 800 annual cases respectively in the United States, often resulting in mild to severe impairments, stillbirths, or neonatal death (Atlaw et al., 2021; Lurie et al., 2023). Globally, more than 260,000 pregnancies are affected by NTDs annually, with 75% of live births resulting in under-five mortality. Most of these cases are folic acid-sensitive and are preventable with adequate periconceptional folic acid intake. The correlation between low folate levels in women of reproductive age and NTD occurrence was first proposed by HibbardHibbard and Jeffcoate (1965), and later confirmed by randomized controlled trials demonstrating the effectiveness of folic acid supplementation in preventing NTDs (Ostrea Jr, 2022).

Genetic variants disrupting folate one-carbon metabolism have been linked to NTDs, with recent studies identifying mutations in folate transporters and receptors (Findley et al., 2017). Polymorphisms in genes related to folate metabolism further increase maternal NTD risk (Cai et al., 2019; Wolujewicz, 2022). Folic acid, a water-soluble vitamin essential for the biosynthesis of amino acids, nucleotides, and neurotransmitters, is critical for cellular growth during pregnancy (Sijilmassi, 2019). Its deficiency is associated not only with NTDs but also with megaloblastic anemia, cancer, cardiovascular diseases, and Alzheimer's disease (Batra et al., 2020).

Neural tube closure occurs within the first 28 days post-conception, often before pregnancy recognition (Atlaw et al., 2021). Folate deficiency may result from inadequate dietary intake, malabsorption (e.g., alcoholism), increased physiological demand, or the use of medications that interfere with folate metabolism (Ebara, 2017). A blood folate concentration below 140 ng/mL defines deficiency, whereas WHO recommends >400 ng/mL to prevent NTDs. Folate plays a critical role in cell division, and its deficiency impairs fetal and placental growth (Tefera et al., 2022). Therefore, WHO recommends folic acid supplementation from conception through the 12th gestational week and promotes balanced energy protein intake in undernourished populations (Alemajo et al., 2022; Young et al., 2022).

Although multiple genetic and environmental factors influence NTD development, folic acid deficiency remains the most preventable cause (Bitew et al., 2020). Environmental factors such as folate intake, gastrointestinal absorption, and exposure to teratogens like antiepileptic or antifolate drugs also contribute. Immune factors, such as folate receptor autoantibodies, have been implicated in NTDs (Wilson, 2022). Studies show that periconceptional folic acid supplementation reduces NTD risk by up to 72% (Argyridis, 2019). A 0.4 mg daily supplement during the periconceptional period can prevent 50–70% of NTDs (Uzun et al., 2023), and targeted nutrition strategies have significantly reduced NTD incidence globally (CoppCavalli and Greene, 2023; WhiteArif-Pardy and Connor, 2023).

Folates (vitamin B9) and derivatives like tetrahydrofolate (THF) are essential for nucleotide synthesis and function as cofactors in one-carbon

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metabolism. Humans cannot synthesize folates endogenously and must obtain them through diet, making them essential micronutrients. Studies show that more than 40% of women of reproductive age globally are folate deficient, contributing to the high annual incidence of NTDs. Supplementation and food fortification are the two primary strategies to combat this deficiency (Maruvada et al., 2020; WangYu and Wang, 2023; Rodrigues et al., 2023).

Natural foods contain reduced forms of folate, while synthetic folic acid, found in fortified foods and supplements, is more bioavailable. Folate-rich foods include legumes, leafy greens, citrus fruits, whole grains, mushrooms, and animal liver (Mutlag, 2019; OtsuAe and Kuwabara, 2023). Governments encourage folic acid supplementation and food fortification to ensure adequate intake during preconception and pregnancy (Ledowsky et al., 2022). Fetal development is significantly influenced by maternal folate status, which also impacts gene expression through epigenetic mechanisms. The recommended daily folate intake increases from 400 mcg to 600 mcg during pregnancy. The 1996 FDA mandate for folic acid fortification of enriched grains in the U.S. resulted in a marked decrease in NTD incidence (Barchitta et al., 2020; Khan et al.).

Approximately 80 countries have adopted folic acid fortification (FAF). The UK initiated public consultation on mandatory flour fortification in 2019 (Morris and Wald, 2023). This approach is part of a broader public health model for preventing spina bifida and anencephaly (SBA) (Shlobin et al., 2022). Due to folate loss during cooking and food processing, dietary intake alone is insufficient, highlighting the importance of widespread food fortification as an equitable, efficient strategy (Kancherla et al., 2022).

Estimates show that mandatory folic acid fortification programs prevented 18% of potential SBA cases in 2017 and 22% in 2019 (Martinez et al., 2021). Many countries now implement national programs to address folate deficiency and reduce folic acid-related illnesses (Kaldygulova et al., 2023). In Pakistan, despite the high burden of NTDs, fortified foods remain inaccessible, and awareness about folic acid remains low. The prevalence of NTDs in Pakistan ranges from 12–14 per 1,000 live births or 38.6–124.1 per 10,000 live births—significantly higher than in developed countries. Factors contributing to inadequate folic acid intake among women of reproductive age include lack of access to antenatal care, limited awareness, cost barriers, cultural resistance, and misconceptions about supplements (Yasmin et al., 2022). There is currently no national awareness program in Pakistan addressing NTD risks or promoting folic acid use. Therefore, the aim of this systematic review is to:

Estimate the prevalence of NTDs globally and within Pakistan

and evaluate the effectiveness of folic acid supplementation and food fortification in reducing NTD risk in other countries.

Review of literature

Neural tube defects (NTDs) are among the most common congenital malformations globally, with significant implications for neonatal morbidity, mortality, and long-term disability. Their prevalence varies by region, often reflecting disparities in nutrition, healthcare access, and awareness of folic acid supplementation. This review synthesizes global data to evaluate the effectiveness of folic acid fortification and supplementation in reducing NTD prevalence.

In Sudan, a hospital-based study by Omer et al. (2016) reported an NTD prevalence of 2.8/1000 among 36,785 newborns, with irregular folic acid intake noted in 57.4% of mothers. In India, Malik et al. (2020) identified a higher rate of 4.3/1000 in a retrospective cohort of 21,187 births. Lu (2023), using Global Burden of Disease data, noted worldwide NTD incidence at 2.1 per 100,000, with India having the highest number of prevalent cases.

In Ireland, McDonnell et al. (2015) reported an incidence of 1.04/1000 births among 225,998 deliveries. Barlow-Mosha et al. (2022) found a notably higher prevalence of 9.8/10,000 in Kampala, Uganda, with spina bifida as the leading type. Similarly, a Nicaraguan study recorded 14.01/10,000 births affected by NTDs, with maternal folic acid use nearly absent (DM et al., 2023).

In Eastern Ethiopia, Berhane and Belachew (2022) reported an incidence of 107.5 per 10,000 live births, with nearly all mothers not using folic acid pre-pregnancy. Another Ethiopian study by Kindie and

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Mulu (2022) revealed a prevalence of 10.9/1000 pregnancies, again noting minimal supplement use.

A meta-analysis by Ssentongo et al. (2022) estimated a pooled NTD prevalence of 33.3/10,000 in Eastern Africa, five times higher than rates in the U.S. The highest national rate was found in Ethiopia (59.74/10,000). In North-Western Nigeria, Nnadi and Singh (2016) reported a prevalence of 2.2/1000, while in South Africa, Krzesinski et al. (2019) identified a birth prevalence of up to 1.18/1000 when accounting for rural under-referrals.

Kant et al. (2017) observed a prevalence of 24.1/10,000 in a North Indian community study. In Addis Ababa, Gedefaw et al. (2018) estimated an NTD prevalence of 126/10,000 births, underscoring regional disparities within Ethiopia. In Iran, Behrooz (2007) reported an NTD incidence of 4.2/1000 in 13,262 pregnancies. The highest global rate, 138.7/10,000, was documented in Shanxi Province, China (Li et al., 2006), where folic acid use was minimal.

Collectively, these studies consistently demonstrate higher NTD rates in regions with limited folic acid supplementation and poor periconceptional coverage. Spina bifida, anencephaly, and encephalocele remain the most reported types. The variation in NTD prevalence emphasizes the critical role of folic acid in prevention and the urgent need for widespread fortification policies and educational interventions

Prevalence of neural tube defects in Pakistan

Neural tube defects (NTDs) represent a major public health concern, especially in low- and middle-income countries, where preventive strategies like folic acid supplementation are underutilized. In Pakistan, birth defects account for 6%–9% of neonatal deaths. A cross-sectional study conducted at Khyber Teaching Hospital in Peshawar found that among 1,062 births, 31 infants had birth defects, with hydrocephalus (22.6%), anencephaly (12.9%), and spina bifida (9.7%) being most common. Only 32.3% of mothers reported using folic acid or multivitamins during pregnancy (Khan et al.).

Khattak et al. (2008) identified 46 NTD cases out of 3,310 deliveries in Peshawar, with hydrocephalus (45.60%) and spina bifida with meningocoele (17.39%) as prevalent types. Remarkably, only one affected mother had taken folic acid—and that too after 20 weeks gestation. In Rahim Yar Khan, a prospective study by Saleem, Ali, and Hussnain (2010) reported 140 NTD cases among 11,655 newborns (12.01/1000), with spina bifida affecting 130 infants. Folic acid supplementation during early pregnancy was found in just 8.6% of cases versus 30% of controls.

A cross-sectional study from Dera Ghazi Khan Tertiary Care Center reported 52 NTD cases among 2,000 live births (2.0% prevalence). Hydrocephalus affected 48.1% of cases, while non-use of folic acid increased NTD risk by 7.8 times. Only 14.9% of mothers reported folate intake during conception (Bokhari and Qureshi, 2020). At Mardan Medical Complex, 117 of 9,453 births involved congenital anomalies, mostly CNS-related. Hydrocephalus (27.3%) and anencephaly (18%) were most frequent, with 71% of mothers not using folic acid and 61.5% of parents reporting consanguinity (Qadir, Amir, and Bano, 2017).

A study at Frontier Medical and Dental College, Abbottabad, examined 12,400 patients, identifying 570 with birth defects, 210 of which were NTDs. Anencephaly (57 cases) and spina bifida (48 cases) dominated. Folic acid use was absent in 438 cases (Rehan Farooqui and Farooqui, 2019). At Military Hospital Rawalpindi, a study compared folic acid users and non-users among 372 pregnancies. NTD incidence was 2.7% in the supplement group and 7.5% in the non-supplement group (Moin, 2013).

In a study at PUMHS, Benazirabad, 38 NTD-affected pregnancies were detected among 7,152 births (5.31/1000). Anencephaly (57.89%) was most frequent, followed by spina bifida with hydrocephalus (31.57%) (Yousuf et al., 2019). At Pak Red Crescent Medical & Dental College, 11% of 200 pregnant women were diagnosed with CNS anomalies. Folic acid use was reported by 56%, while 44% had low or no folate intake (Nahra et al.). At Hayatabad Medical Complex, Peshawar, 18 NTD cases were identified among 3,350 live births (5.3/1000), with hydrocephalus and multiple NTDs prevalent. Only one mother reported folic acid intake, initiated post-20 weeks (Nawaz, Qazi, and Safi, 2014).

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Effectiveness of folic acid fortification & supplementation in the prevention of NTDs

Globally, over 70 countries including the U.S., Canada, and Australia have implemented mandatory folic acid fortification. Supplementation before conception can reduce NTD risk by up to 72%. However, dietary intake alone is often insufficient. Bestwick et al. (2014) observed a decline in preconception folic acid use from 40% in 1999–2001 to 28% in 2011–2012. Clinical trials and observational studies affirm that daily supplementation (400mcg to 4mg) and fortified food significantly reduce NTD incidence. The U.S. introduced flour fortification in 1998, prompting over 60 countries to adopt similar measures.

Castillo-Lancellotti, Tur, and Uauy (2013) reviewed 27 studies, with 15 showing reduced NTD rates post-fortification—most notably a 58% drop in Costa Rica and a 15.5% reduction in California. Rosenthal et al. (2014) noted an annual 6% decline in Latin American countries after fortification. In Chile, the prevalence fell from 17.1 to 8.6 per 10,000 live births post-fortification at 2.2 mg/kg (Pardo et al., 2022).

Israel saw a 45% reduction in NTDs after implementing supplementation policies and maintaining a national registry (Reiss et al., 2020). Dean, Pauly, and Stevenson (2020) reported a significant NTD prevalence reduction in South Carolina from 1.3/1000 pre-fortification to 0.56/1000 post-fortification. Canada recorded a 46% reduction post-fortification (De Wals et al., 2007), while the U.S. multi-state initiative showed similar success (Canfield et al., 2014). Rakaf et al. (2015) documented a prevalence of 1.7/1000 from a case–control cohort of 2,441 mothers.

However, not all countries have achieved significant reductions. In Lima, Peru, NTD prevalence remained relatively unchanged at 20.0 to 18.4 per 10,000 births post-fortification (Ricks et al., 2012). Australia mandated flour fortification in 2009 and reported a reduction, while New Zealand approved fortification only in 2021 after prolonged debate (Thurston, Borman, and Bower, 2023). In Saudi Arabia, prevalence decreased from 1.46 to 0.81 per 1000 live births after flour fortification (Seidahmed et al., 2014). Similarly, North Jordan saw a decline from 1.85 to 0.95 per 1000 deliveries post-fortification (Amarin and Obeidat, 2010).

These studies confirm that folic acid fortification and supplementation are cost-effective, evidence-based interventions with significant potential to prevent NTDs. However, disparities in coverage, awareness, and policy implementation, particularly in developing countries like Pakistan, underscore the need for sustained public health efforts and further research.

Methodology

The literature search was performed using Medline via PubMed, Sci-Hub, and Google Scholar. The search strategy employed a combination of keywords, including: “neural tube defects,” “spina bifida,” “anencephaly,” “encephalocele,” “folic acid,” “folate deficiency,” “congenital anomalies,” “hydrocephalus,” “folic acid fortification,” “folic acid supplementation,” “neural tube defects’ prevalence,” “neural tube defects etiology,” “nutritional deficiency,” and “folate fortified foods.” These keywords were used to identify studies in which titles or abstracts indicated a focus on the relationship between folic acid and the prevalence or prevention of neural tube defects.

To enhance the comprehensiveness of the review, relevant studies were also identified through the reference lists of previously published articles, systematic reviews, and meta-analyses. The aim was to capture all pertinent research that assessed either the prevalence of NTDs or the preventive effects of folic acid fortification and supplementation.

The review incorporated various study designs, including case-control studies, cross-sectional studies, retrospective studies, supplementation trials, and reports that documented the prevalence of NTDs—specifically defined as anencephaly, spina bifida, or encephalocele. Studies evaluating the impact of folic acid interventions on the prevalence of these conditions were included. Furthermore, studies reporting NTD prevalence without explicitly defining the diagnostic criteria were also considered, in order to broaden the scope of the available data. Exclusion criteria included studies that exclusively focused on individual NTD subtypes (e.g., only anencephaly or spina bifida) without a broader NTD context, as well as studies addressing only non-NTD congenital malformations.

The initial search yielded a total of 1,185 published articles. After removing 250 duplicate records, 935

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unique articles and abstracts were screened against the inclusion and exclusion criteria. Of these, 370 abstracts were excluded during the preliminary review. A detailed full-text screening was conducted for the remaining 565 citations. Following this second phase of evaluation, 504 additional studies were excluded for not meeting the defined criteria.

Ultimately, 61 unique studies and reports published between March 2006 and April 2023 were identified as relevant. After final assessment, 37 studies were selected for inclusion and critical analysis in this review. Although several studies on the prevalence of neural tube defects have been conducted within Pakistan, there is a noticeable absence of research assessing the impact of folic acid fortification and supplementation in this context. Consequently, the present systematic review incorporates and synthesizes findings from international studies to evaluate the effectiveness of fortification strategies and folic acid supplementation before and during pregnancy in reducing the risk of NTDs globally.

Table 01: Selected studies on prevalence of NTDs in different countries around the World

Study Area	Sample size	NTDs/1000 livebirths	Spina bifida	Anencephaly	Encephalocele	References
Khartoum, Sudan	36,785	100	49	18	14	Omar et al. (Omer et al., 2016)
Rohtak, India	21,187	90	39	40	5	Malik et al. (Malik et al., 2020)
Ireland	225,998	236	115	106	15	McDonell et al. (McDonnell et al., 2015)
Kampala, Uganda	110,752	109	63	31	15	Barlow et al. (Barlow-Mosha et al., 2022)
Nicaragua, Central America	178,498	250	140	97	13	DM Pastora et al. (DM et al., 2023)
Debre Berhan, Ethiopia	1000	97	31	50	10	Kindie & Mulu. (Kindie and Mulu, 2022)
North-western Nigeria	10,163	22	16	5	1	Nnadi et al. (Nnadi and Singh, 2016)
South Africa	1000	195	108	59	28	Krzesinski et al. (KrzesinskiGeerts and Urban, 2019)
Faridabad, Haryana	26,946	140	69	33	26	Kant et al. (Kant et al., 2017)
Addis Ababa, Ethiopia	8,677	126	51	68	7	Gedefaw et al(GedefawTeklu and Tadesse, 2018)
Ahvaz, Iran	13,262	56	15	30	3	Behrooz, (Behrooz, 2007)
Shanxi, China	11,534	143	52	66	15	Li et al. (Li et al., 2006)

Table 02: Selected studies on prevalence of NTDs in Pakistan

District	Sample size	Total NTDs with or without hydrocephalus	Spina bifida	Anencephaly	Encephalocele /meningomyelocele/ meningocele	References
Peshawar	3,310	46 (21 with hydrocephalus)	8	6	11	Khattak et al. (Khattak et al., 2008)
Rahim Yar Khan	11,655	140	130	4	6	Saleem et al. (SaleemAli and Hussnain, 2010)
Dera Ghazi Khan	2,000	52 (25 with hydrocephalus)	10	6	9	Bokhari & Qureshi, (Bokhari and Qureshi, 2020)
Mardan	9,453	117 (92 with hydrocephalus)	13	21	19	Qadir et al. (QadirAmir and Bano, 2017)
Abbotabad	12,400	210	48	57	33	Rehan et al. (RehanFarooqui and Farooqui, 2019)
Rawalpindi	372	19	-	-	-	Moin et al. (Moin, 2013)
Benazirabad	7,152	38 (with hydrocephalus)	12	22	4	Yousuf et al. (Yousuf et al., 2019)
Kasur	200	11 (with hydrocephalus)	5	6	-	Nahra et al. (NAHRA et al.)
Peshawar	3,350	18 (8 with hydrocephalus)	3	2	5	Nawaz et al. (NawazQazi and Safi, 2014)

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Table 03: Studies on Folic Acid fortification (Systematic Review)

Studies	Country	Focus of investigation	Results
Bestwick et al. (Bestwick et al., 2014)	United states Canada Australia	Assessed the extent of folic acid supplementation before pregnancy	Reduced the risk of NTD affected pregnancy by an estimated 72%
Lancelottiet al. (2013)	California Costa Rica	FDA mandated that flour be fortified with folic acid to ensure adequate supply of folate to women of child-bearing age	Drops were observed in NTDs in Costa Rica (58%) and in California (15.5%) in response to fortification
Rosenthal et al. (Rosenthal et al., 2014)	Latin America	Consumption of staples fortified with folic acid and peri-conceptional folic acid supplementation	NTD prevalence varied from 9.6 to 0.2 per 1000 live births in Latin American countries.
Pardo et al. (Pardo et al., 2022)	Chile	Fortification of wheat flour with folic acid at concentration of 2.2mg/kg to prevent NTDs	Resulted in 50% reduction of NTDs From 17.1 to 9.5 & 8.6 per 10,000 live births from 2010 to 2015

Prevalence of Neural Tube Defects (NTDs) Around the World

This systematic review analyzed a total of 37 studies to assess the global and national burden of neural tube defects (NTDs), with particular focus on prevalence and prevention. Despite increased awareness over the past three decades about the preventative role of folic acid, NTDs remain a significant global concern. Preventing these defects is vital due to their devastating consequences, both in terms of individual disability and public health costs. The widespread use of antenatal ultrasound has enabled early diagnosis and termination of affected pregnancies, thereby reducing the incidence of NTDs among live births.

Out of the 37 selected studies, 16 addressed the global prevalence of NTDs. These studies collectively estimate that over 260,000 pregnancies worldwide are affected by NTDs. A meta-analysis conducted by Blencowe et al. (2015) concluded that NTD prevalence remains high in many low and middle-income countries, despite improvements in healthcare infrastructure. Zaganjoor et al. (2016) similarly reported a wide range in prevalence, from as low as 0.3 to as high as 199.4 per 10,000 live births. Across the studies included in the current review, a cumulative sample of 645,802 live births was reported, with 1,564 NTD cases identified.

Among studies providing data stratified by NTD subtype, spina bifida consistently emerged as the most prevalent form, followed by anencephaly and encephalocele. Ssentongo et al. (2022) found that Ethiopia exhibited the highest birth prevalence of NTDs at 59.74 per 10,000 live births, with Eritrea closely following, while Malawi showed the lowest rates. Their findings underscore that the combined prevalence of NTDs in Eastern Africa is nearly five times that of the United States post-fortification era.

Prevalence of NTDs in Pakistan

In Pakistan, congenital anomalies contribute to 6% to 9% of perinatal mortality. Masood et al. (2011) reported an NTD prevalence of 11.4 per 10,000 live births, with these defects accounting for 65.8% of all congenital anomalies. Similarly, Khattak et al. (2008) observed a prevalence of 12.14 per 10,000 live births. Spina bifida and anencephaly were the most frequently observed NTDs, followed by encephalocele. Notably, hydrocephalus co-occurred in approximately 72% of NTD cases. A synthesis of ten studies from Pakistan reported 651 cases of NTDs with hydrocephalus out of 49,892 live births.

Peri-conceptional folic acid supplementation has consistently demonstrated up to a 70% reduction in NTD risk. According to the Centers for Disease Control and Prevention (CDC), approximately 75% of spina bifida cases could be prevented through adequate folic acid intake. Historical evidence by Hibbard and Jeffcoate (1965) first established the association between low folate levels in women of reproductive age and increased NTD risk. This review confirms the critical role of folic acid during early gestation, especially considering that neural tube closure occurs by the 28th day of pregnancy—often before pregnancy is even recognized. Data from the reviewed studies clearly show that the prevalence of

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NTDs is substantially higher among populations not using folic acid supplementation.

Effectiveness of Folic Acid Fortification and Supplementation

Following the global and national review of prevalence, this study examined the impact of folic acid fortification and supplementation in reducing NTD incidence. Fortification is a technically feasible public health strategy, particularly when folic acid is incorporated into pre-mixed formulations already used in the fortification of flour with other micronutrients such as iron, zinc, and B vitamins as demonstrated in countries like Chile. However, localized research is needed to establish optimal fortification protocols in Pakistan, particularly for ensuring nutrient uniformity in flour mills and small-scale production units.

The dosage of folic acid necessary for effective NTD prevention has been examined in detail. Wald (2022) conducted a meta-analysis indicating a dose-dependent protective effect: a 0.2 mg/day intake was associated with a 23% reduction in NTD risk, 0.4 mg/day with a 36% reduction, and 5 mg/day with up to 85% reduction. Notably, countries with higher baseline rates of NTDs tend to show greater absolute benefits from folic acid interventions. For instance, in Nova Scotia, Canada, the number of open NTDs dropped from 30 cases in 1991 to just 9 in 2000—a 70% reduction following fortification efforts.

In the Middle East, Amarin and Obeidat (2010) documented a significant reduction in NTD prevalence in North Jordan, from 1.85 per 1,000 live births prior to folic acid fortification, to 1.07 during the intervention period, and further to 0.95 per 1,000 post-fortification. This represented a substantial 49% decline in overall NTD incidence, highlighting the measurable impact of long-term public health fortification initiatives.

These findings collectively underscore the effectiveness of both folic acid supplementation and mandatory food fortification as viable, evidence-based strategies to significantly reduce the global burden of NTDs. Continued policy support, implementation of mandatory fortification programs, and increased awareness regarding peri-conceptional folic acid use remain essential, particularly in low- and middle-income countries where the burden remains disproportionately high.

Conclusion

This systematic review provides compelling evidence on the substantial burden of neural tube defects (NTDs) globally and nationally, with a focus on Pakistan, and the proven efficacy of folic acid supplementation and fortification in reducing their incidence. Despite decades of research demonstrating the critical role of folic acid in neural tube development, NTDs remain prevalent, particularly in low- and middle-income countries where food fortification policies are either absent or inconsistently implemented.

The findings consistently show that folic acid supplementation, particularly during the peri-conceptional period, can reduce NTD risk by up to 70%, and large-scale food fortification programs have significantly lowered NTD prevalence in countries such as Canada, the United States, Chile, and Jordan. However, many countries, including Pakistan, have yet to implement effective nationwide fortification strategies or achieve sufficient coverage of folic acid use among women of reproductive age.

A major barrier remains the delayed intake of folic acid, as many pregnancies are unplanned and supplementation often begins after neural tube closure has already occurred. This highlights the need for mandatory fortification of staple foods, public health education, and strengthened healthcare systems that prioritize maternal nutrition as part of routine reproductive health services.

Recommendations

Based on the findings of this review, it is strongly recommended that countries with high neural tube defect (NTD) prevalence, such as Pakistan, urgently implement mandatory folic acid fortification of staple foods like wheat flour to ensure adequate population-wide intake. Public health strategies should focus on promoting peri-conceptional folic acid supplementation among women of reproductive age, integrating folic acid distribution into maternal and child health services, and enhancing public awareness through culturally appropriate education campaigns. Establishing national birth defect surveillance systems is crucial to monitor NTD trends and evaluate

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intervention outcomes. Moreover, intersectoral collaboration among health authorities, policymakers, and food industries is essential to design, implement, and sustain effective folic acid fortification programs that can significantly reduce the burden of NTDs and improve neonatal health outcomes

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