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Fortifying the Future: Urological Perspectives on Folic Acid and Spina Bifida Prevention

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ABSTRACT

Introduction: Spina bifida affects 214,000-322,000 pregnancies globally every year. The incidence of this permanently disabling, yet preventable, neural tube defect is 1 in 500 births worldwide but disproportionately 1 in 100 births in low- and middle-income countries. Large-scale food fortification of folic acid, passed in 2023 by the World Health Assembly, provides an economically safe and equitably sustainable public health strategy to prevent the life-long urology-associated manifestations of spina bifida.

Methods: A literature review was conducted to explore the role of folic acid fortification in preventing spina bifida in the context of urological care.

Results: The estimated lifetime direct costs of spina bifida, as it relates to urological care, range between $500,000-$791,900. The goal of urological care in spina bifida patients is to maximize functional status. Folic acid fortification has resulted in fewer cases of spina bifida and consequently fewer pediatric and adult spina bifida-associated urology surgeries. Furthermore, folic acid fortification in the prevention of spina bifida has demonstrated better economic, psychosocial, and health outcomes.

Conclusion: Through research, public health initiatives, and campaigns, widespread folic acid fortification has played a crucial role in reducing spina bifida-related urological morbidity and mortality. Spina bifida is preventable, along with its associated psychosocial, economic, medical, and financial burdens. Currently, there are no global consensus guidelines on spina bifida prevention. Hence, government and healthcare organizations are encouraged to support the World Health Assembly resolution in preventing spina bifida through large-scale folic acid fortification.

Abbreviations: CIC = clean intermittent catheterization; LMIC low- and middle-income country; LUT = lower urinary tract; MMC = myelomeningocele; MOM = management of myelomeningocele; NB = neurogenic bladder; NTD = neural tube defect; SB = spina bifida; UTI = urinary tract infection; VUR = vesicoureteral reflux

Keywords: spina bifida, spinal dysraphism, folic acid, prevention, urologic

INTRODUCTION

Spina bifida (SB), a neural tube defect, is one of the most common permanently disabling yet preventable birth defects. Annually, around 214,000 to 322,000 pregnancies globally are associated with SB and anencephaly, or a prevalence of 1 per 500 live births.[1] Low- and middle-income countries (LMICs), however, suffer a prevalence of SB and anencephaly-associated pregnancies at a rate of 1 in every 100 births, which is disproportionately greater than the prevalence for all births worldwide.[1] Individuals living with SB receive lifelong medical and surgical care for urologic, neurologic, orthopedic, and psychological sequelae.[2] Moreover, surgical care may be unavailable or unaffordable for those who live in LMICs.[3]

An inadequate maternal concentration of folate is the primary cause of SB.[4] During the first 28 days of pregnancy, folic acid is required for proper neural tube closure. Prenatal folic acid supplement pills are recommended as an adjunct to a healthy, folate-rich diet of dark, leafy green vegetables; however, supplements have low adherence rates and, given that nearly half of all pregnancies are unplanned, are often started after the critical 28-day period.[3,5,6] Large-scale folic acid fortification of staple foods is an economical, equitable, safe, and sustainable solution to prevent SB that was recently adopted at the 2023 World Health Assembly.[3,7]

Urologic manifestations of SB include neurogenic bladder (NB) with symptoms like urinary incontinence, urinary tract infections (UTIs), and renal failure; and sexual dysfunction, which includes erectile dysfunction and impaired genital sensation and orgasm.[8,9] The primary objectives of urological care for patients with SB are social continence, preservation of renal function, and sexual counseling.[8] Various medical and surgical therapies are used to accomplish these goals including clean intermittent catheterization (CIC), anticholinergic drugs, intradetrusor botulinum toxin injection, and bladder/urinary tract reconstruction.[10,11] Mandatory folic acid fortification has the potential to eradicate most cases of SB and its associated costs, such as lifelong healthcare expenses and psychosocial consequences.

METHODS

The PubMed/MEDLINE (National Library of Medicine) database was queried on May 29, 2023, for articles published in or translated into English, using the terms "spina bifida" OR "neural tube defect", in combination with "urology", "urologic", "urological", "bladder", "urinary", "sexual", "renal", or "kidney". The rationale behind these search terms was to investigate the correlation between folic acid fortification and the urological management of patients with SB. No publication date restrictions were applied, allowing for a thorough and up-to-date review of literature.

Following the initial search, articles were screened for relevance to the research question, excluding those that did not align with the study’s objective. Selected articles were then assessed for quality through a meticulous review of their abstracts to identify key findings and relevance.

The final selection included articles that discussed the role of urology in SB care related to folic acid fortification, as well as those examining the psychosocial, economic, and health impacts of SB.

DISCUSSION

Spina Bifida Etiology

SB is characterized by incomplete closure of the spinal column during early fetal development. This results in severe lifelong morbidity causing many women to terminate their pregnancy after prenatal detection.[12] While the etiology of many cases of SB remains unknown, contributing factors may encompass chromosomal abnormalities, single-gene disorders, and exposure to teratogens.[10]

The etiology of SB is multifactorial, involving both genetic and environmental factors. Genetic factors, such as having a family member with a neural tube defect (NTD), increase your chances of having a baby with SB. One of the major environmental causes of this disease is folic acid deficiency during pregnancy.[10] To address this deficiency, folic acid fortification programs were implemented worldwide, which resulted in a significant decrease in the incidence of SB and reduced the risk of urological complications such as NB, urinary incontinence, and UTIs in individuals with SB.[11]

Spina Bifida in Urology

Spina Bifida and Organ System Involvement

The United States National Spina Bifida Patient Data Registry describes SB as the most common cause of congenital neurogenic lower urinary tract (LUT) dysfunction due to neuropathy sphincter and/or bladder. Furthermore, this neurogenic dysfunction limits normal morphology and function.[12] NB can create a high-pressure environment that results in vesicoureteral reflux (VUR), or the retrograde flow of urine from the bladder to one or both ureters and even the renal pelvis.[13-15] VUR can damage upper urinary tract structures and lead to renal insufficiency and end-stage renal disease.[16]

Treatment Approach

Lifetime multidisciplinary follow-up is crucial for patients with NB to preserve renal function and optimize their quality of life.[15] Treatment goals focus on improving quality of life, preserving upper urinary tract function with good renal/bladder reservoir, and preventing UTIs through effective bladder management.[17] The European Association of Urology (EAU) and the European Society for Paediatric Urology (ESPU) recommend CIC and/or anticholinergic medications within the first few months of life.[17] However, research by Wiener et al. indicates that despite a higher prevalence of NB among individuals with myelomeningocele, many children, adolescents, and adults manage their condition using voluntary voiding.[12]

Träff et al.[13] also investigated patient-reported morbidity from NB management with CIC or anticholinergic medication, finding that a third of patients still experienced symptoms like leakage. Evidence on UTI prevention strategies remains unclear.[13] Moreover, healthcare workers often lack knowledge about established treatments for SB-related VUR and follow-up guidelines.[18]

The Management of Myelomeningocele (MOM) study trial by Le et al.[19] concluded that patients who underwent prenatal and postnatal repair of myelomeningocele showed similar urodynamic changes. Additionally, the implementation of advanced bladder management strategies and UTI treatments has led to a decline in NB related mortality in children with SB.[14]

Sexual Dysfunction

Sexual health is described by the World Health Organization as a state of emotional, physical, social, and mental well-being concerning sexuality, which requires a respectful and positive approach to sexual relationships and sexuality.[20] According to Streur et al.[21], about half of SB adults are sexually active, which may be influenced by the type and level of the defect/lesion. In the international online survey done by Szymanski et al.[22] on male sexual function with SB, 36% had a rigid penis with erections, 69% experienced orgasms, and 84% ejaculated during sexual intercourse.

There is very limited literature on the multifactorial etiologies concerning sexual dysfunction among individuals with SB.[9,21,22] Large multi-center studies may help in better understanding sexual function evaluation and prediction in SB men and women. Moreover, there is even less understanding of and no treatment for female sexual dysfunction as it relates to SB.

Pathophysiology

Sexual dysfunction in SB individuals is due to sacral spinal cord malformation with the disruption of the thoracolumbar (T11-L2) sympathetic innervation pathways input and pelvic plexus cerebral disruption for descending control, which is possibly responsible for genital arousal, orgasm, and ejaculation. Individuals with these disruptions may present with varying motor and sensory functions.[9,22]

Medical and Surgical Management

The life expectancy of individuals with SB has improved due to advanced surgical and medical management. While 69-95% of SB patients report poor-quality erections, ambulation is linked to better sexual function.[4] Better-tailored care can be provided to address individual sexual challenges related to SB.[9] Bladder procedures for NB also contribute to social and emotional well-being, enhancing sexual health. [3] For males, treatments may include evaluating vacuum erection devices, intracavernosal injections, and potential orgasmic and ejaculatory dysfunction.[21]

Spina Bifida Transition of Care

While advanced diagnostic and therapeutic modalities have improved survival to adulthood by 80%, the transition of care to adulthood remains below 50%.[19,23] These patients face multisystem issues that degenerate with age, requiring specialized attention due to the complexity of the condition.[24]

Birth

SB is linked to increased infant and neonatal mortality. Treatment typically involves surgically closing the open NTD, either prenatally (in utero) or postnatally. In urology, infants undergo renal ultrasounds to evaluate renal pathology, hydronephrosis, UTIs, and catheterization issues.[25]

Child

Throughout early childhood, patients with SB are closely monitored by their parents and coordinated, multidisciplinary pediatric clinics, resulting in long-term renal health benefits through regular ultrasounds and urodynamic testing. As patients begin school and extracurriculars, achieving continence becomes a key focus of their treatment.[26] Studies indicate that CIC is the most effective method for gaining continence and managing neurogenic bladder changes, alongside options like anticholinergic pharmacotherapy and surgery.[27]

Adolescent

As children transition to adolescence, care education shifts to independent medication management, follow-up appointments, and daily living management. Medical teams are vital in teaching SB patients about preventative care and disease management. Early conversations help patients and caregivers understand their responsibilities, acquire necessary skills, and clarify future needs. [25]

Adult

After turning 18, patients with SB face challenges in maintaining consistent medical care, as they must visit multiple specialists (neurology, urology, gastroenterology, orthopedics) resulting in a fragmented healthcare system.[27] During this transition, many young SB adults tend to seek care at emergency departments instead of specialty providers, leading to unnecessary hospital visits. A study found that emergency room visits for UTIs were significantly higher in 20-24-year-olds compared to 15-19-year-olds with SB, highlighting the importance of regular follow-ups with urologists. Improving access to comprehensive specialist care could reduce non-urgent emergency room visits.[24]

Psychosocial aspect of Spina Bifida

Patients

Psychosocial development is an area of significant delay for youth with SB. Due to cognitive impairments, they rely heavily on their support systems, increasing their risk of social conflicts, lower employment opportunities, and cognitive challenges.[28] These individuals typically demonstrate reduced behavioral and physical autonomy, which can negatively affect their self-concept. Children with SB often crave social acceptance and harbor fear about their future, worrying about being a burden due to incontinence.[28] While the psychosocial aspects of sexual dysfunction in SB patients are not fully understood, it’s reasonable to assume that lack of privacy and low self-esteem can hinder psychosexual development, as sexual growth is an integral part of overall social development.[21]

Caregivers

Caregivers, typically parents, play a crucial role in the growth and development of SB patients. The significant physical and financial burdens of caregivers can lead to feelings of isolation, social limitations, and high stress levels, often resulting in diminished optimism about the future.[29] The invasive nature of catheterization, which is time-consuming and physically demanding, can further restrict caregivers’ ability to travel or leave home without essential supplies.[30]

Families

A child with SB can disrupt typical family dynamics, with families often developing resilience but struggling to maintain clear roles and responsibilities. [29] Siblings may experience emotional distress from bullying and missed activities, while cultural attitudes towards disabilities can either exacerbate isolation in stigmatizing societies or provide greater support in inclusive ones. [31, 32]

Cost of Spina Bifida

Families of SB patients face lifelong financial challenges, with direct medical costs in the U.S. ranging from $500,000-791,900.[2,33,34] These costs are compounded by indirect social and emotional burdens. The transition from pediatric and adult medical care often goes overlooked, leading to preventable conditions. A 1994 study by Kaufman et al. found that after multidisciplinary clinics for SB patients closed, 45% to 66% of the patients lost consistent care, resulting in missed treatments and higher financial burdens.[35]

Indirect costs, such as lost productivity, caregiver time, and social benefits, often surpass direct medical expenses.[36] While net cost savings per averted case of SB can be 48% over medical expenses, caregivers frequently prioritize their children’s needs regardless of cost, often worrying about the financial implications later.[37]

Economic Benefit of Folic Acid Fortification

Folic acid fortification is a crucial public health policy for preventing SB and associated urologic challenges, leading to significant cost savings.[38] The estimated cost of preventing one death through mandatory fortification is just US$957, and the cost per disability-adjusted life year is $15, comparable to other essential interventions like rotavirus vaccines and insecticide-treated bednets for malaria.[38]

The USA, as the pioneer of mandatory fortification, saw a notable decrease in NTD-related pregnancies after the FDA’s implementation of folic acid fortification in enriched cereal grains. [39] Countries like Chile and South Africa also report impressive benefit-to-cost-ratios of 11.8:1 and 30:1, respectively.[40] Studies show consistent success in nations like Costa Rica, Brazil, and Mexico, with NTD prevalence dropping by 30-31% in Brazil and South Africa, and 58-59% in Costa Rica and Mexico.[41] Even in less favorable scenarios, the investment in mandatory fortification yields nearly equal returns at a rate of 1:0.98, proving all dosages to be cost-effective with positive health outcomes.[36]

Globally, not all countries have adopted mandatory folic acid fortification. The UK has implemented voluntary policies, while many others lack any fortification measures.[42] Philanthropic and governmental efforts have not prioritized this issue, particularly in low- and middle-income countries (LMICs), where poverty limits access to processed foods.[43] This lack of support hampers LMICs' ability to meet child mortality reduction goals set in the 2030 Sustainable Development Agenda.[44]

Currently, more than 80 other countries have adopted the US policy of fortifying cereal grains with folic acid.[42] It is clear that the economic benefits are significant; reducing SB will avert direct and indirect costs.

Call to Action

The recent passing of resolution WHA 76.19 (‘*Accelerating efforts for preventing micronutrient deficiencies and their consequences, including SB and other neural tube defects, through safe and effective food fortification*’) at the World Health Assembly presents an opportunity to significantly reduce urologic morbidity and mortality for patients with SB.[7] Folic acid has proven to prevent neural tube defects and is a cost-effective method of primary prevention.[4,45] However, supplementation alone is insufficient, as the neural tube closes early by day 28 in gestation, and SB can often only be detected in the second trimester. Public health campaigns aimed at encouraging pregnant women to take folic acid to prevent SB often come too late because many women may not realize they are pregnant at that point.[10,14] The resolution signals a global commitment to the health of citizens worldwide.

The urgency in folic acid fortification also lies in the uncertainty of the lifelong burden of SB for healthcare systems that are either ill-equipped and/or overburdened to address the growing number of patients with chronic medical and rehabilitative needs.[10] In a study identifying the concerns of 100 patients with SB and providers, care coordination (eg. referral to other services, rehabilitation) was the top concern.[46] Increasing SB prevalence as patients are living longer will present new complexities in management and treatment will require more expensive and specialized care, furthering the economic burden in nations with emerging healthcare systems.[47]

Food fortification has become a regular practice in high-income nations since the 1920s, with the iodization of salt to combat thyroid disease. Many nations have passed legislation for iodized salt fortification.[48] Evidence strongly supports food fortification as an effective strategy for addressing folic acid deficiency and preventing NTDs. Yet, many countries, particularly LMICs, hesitate to implement mandatory fortification programs due to a perceived lack of conclusive data. Increased monitoring of NTDs and folic acid delivery can provide the necessary data to tailor fortification programs to specific needs. [49,50]

While the resolution does not mandate food fortification, it signals a shift in government priorities. Engaging key stakeholders is necessary to see its widespread adoption of folic acid fortification in a timely and attainable fashion. As governments draft legislation and prepare infrastructure for implementation, the private sector can play a key role in voluntary fortification. Voluntary fortification occurs when food processors add nutrients at their discretion, though studies have shown that without government involvement, such programs may not significantly reduce NTDs.[49,40]

The resolution also calls on the medical community to act. Urologic and obstetric organizations can support the resolution by lobbying for folic acid fortification legislation, strengthening prenatal care recommendations, and providing resources and information regarding SB and NTDs.[50] Engaging a broad range of stakeholders—including students, employees, and public health officials—is crucial for success.

With the resolution now passed, the responsibility lies not only with governments and organizations, but with all members of society. All stakeholders can make significant contributions toward the adoption of this policy. This article supports the passing of the resolution and calls for a multinational, multi-sectoral effort to decrease the incidence of SB and mitigate the burden of complex medical care for patients living with SB by advocating for and working towards implementing folic acid fortification globally.

CONCLUSION

SB is a significant and preventable birth defect that affects a substantial number of pregnancies worldwide. The prevalence of SB is disproportionately higher in LMICs, where access to surgical care and medical facilities may be limited. As a complex congenital NTD, SB leads to various urologic, neurologic, orthopedic, and psychological challenges throughout an individual’s life. Treatment options for managing NB, a common complication associated with SB, remain uncertain, highlighting the need for further research and consensus guidelines.

Approximately half of all global cases of SB are projected to result in either early termination of pregnancy for anomalies (eTOPFAs) or stillbirths. These outcomes often remain unseen by policymakers. The consequences of NTDssignificantly impact mothers, families, and society, forcing difficult decisions about whether to proceed with a pregnancy affected by NTDs. This leads to emotional burdens following stillbirth or eTOPFA, while also presenting financial and logistical challenges in caring for a child with complex needs stemming from NTDs.[1]

The psychosocial impact of SB cannot be overlooked, as patients often face depression, isolation, educational setbacks, and social maladjustment. The burden of disease extends beyond the individual to their caregivers and families, who endure emotional and financial hardships while caring for a child with SB. The economic cost of SB is substantial, encompassing direct medical expenses, long-term management, therapy, and indirect costs that affect both the patient and their family.

However, there is hope due to folic acid fortification. Studies have shown that folic acid is a cost-effective method of preventing NTDs, including SB. The recent resolution passed at the World Health Assembly focused on preventing micronutrient deficiencies and neural tube defects through food fortification, offers a significant opportunity to reduce the urologic morbidity and mortality associated with SB.[2,7] By encouraging the widespread use of folic acid, public health campaigns can play a crucial role in preventing SB and improving the health and well-being of future generations.

The fight against SB requires collective commitment and investment from national and global organizations to ensure access to preventative measures and adequate medical care for affected individuals. Through continued research, improved treatment options, and public health initiatives, we can work towards a world where SB is no longer a prevalent and disabling birth defect, and where all individuals have the opportunity to lead healthy and fulfilling lives.

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