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Folic acid prescription practice for high-risk prevention of spina bifida at a tertiary care hospital in Addis Ababa, Ethiopia

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Abstract.
PURPOSE: Mothers who have had a pregnancy affected by spina bifida are advised to take 4-5 mg/day folic acid pills to prevent recurrence. The folic acid prescription pattern was examined for high-risk mothers whose children received spina bifida surgery in an urban Ethiopian hospital.
METHODS: Data were analyzed from a large Ethiopian urban tertiary care hospital that provided spina bifida care. General practitioners recorded 5 mg/day folic acid prescriptions administered to mothers of infants with spina bifida born between January 2019 and June 2022.
RESULTS: Among 500 baby-mother pairs, 340 (68%) received a 120-day prescription for 5 mg/day folic acid pills. Of these 340 mothers, 331 (97%) received their folic acid prescription at their child's first or second patient encounter. Almost all mothers (94%) had documentation of only one prescription for the study duration. The percentage of mothers receiving at least one prescription varied by the baby's year of birth (2019:75%; 2020:92%; 2021:46%; Jan 2022 – June 2022:79%).
CONCLUSION: This prioritization of spina bifida recurrence prevention demonstrates feasibility for other healthcare centers in low-income countries. Sustained funds to provide women with free folic acid pills can favor high compliance and uptake of this prevention intervention.

Keywords: Neural tube defects, spina bifida, congenital anomalies, folic acid, high risk prevention

1. Introduction

Neural tube defects (NTDs), largely comprised of spina bifida and anencephaly, are the second most common birth defects worldwide and result in severe morbidity and mortality among those affected [1]. Women who have had a pregnancy affected by an NTD have a high risk of recurrence in a subsequent pregnancy, estimated at about 3% [2]. In pooled data from eight testing centers with 831 pregnancies in the USA, the recurrence risk for patients with one prior pregnancy affected with an NTD was 3.0%, with 95% confidence limits of 2.0–4.3% and 99% confidence limits of 1.8–4.8% [3]. In a genetic counselling study in Hungary from 1969, the recurrence of the multifactorial form of isolated NTDs was 3.4 % [4]. In 1991, a double-blind randomized trial conducted by the British Medical Research Council proved

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unequivocally the protective effect of pre-pregnancy folic acid supplementation. A dose of 4 mg/day provided a 72% reduction in the risk of recurrence of NTDs in women with a previous pregnancy affected by an NTD [5].

Current recommendations promote a 4–5 mg daily oral folic acid supplement for at least three months before conception and until 12 weeks gestational age for women with an increased or high risk for NTDs, for women who have a male partner with a personal history of NTDs, and for those with a history of a previous NTD-affected pregnancy [6]. Further, a robust review of the literature confirmed that no prior examination or laboratory evidence is needed prior to initiating folic acid supplementation for women at high risk for a recurrent NTD-affected pregnancy [6]. The most current guidelines published by the Spina Bifida Association recommend counseling women about their recurrence risk, and they promote a 4 mg/day folic acid supplement for at least one month, but preferably three months, prior to conception, to continue through the first three months of pregnancy [7]. Interestingly, a previous study has also shown an NTD recurrence rate in partially supplemented mothers (vitamins started at conception or up to day 26 post-conception) of 0.94%, indicating practitioners should attempt to give supplementation before the estimated date of neural tube closure even if full supplementation cannot be done [8].

Few countries have undertaken recurrence prevention programs for NTDs. One of the early studies, reported by Czeizel et al., highlighted a national program promoting folic acid to high-risk mothers, aiming at averting NTD recurrence risk in Hungary [9]. Currently, even within high-income countries such as the United States and Canada, very few states have birth defects surveillance programs that engage in recurrence prevention activities, and this is largely attributed to lack of allocated resources [10]. Two US-based studies showed the benefit of recurrence prevention programs in the US. Felkner et al. studied 130 Mexican-American women who received folic acid supplementation, and 0% recurrence occurred in the group, which considered both live and adverse pregnancy outcomes [11]. Similarly, Bupp et al. used birth defects surveillance data from South Carolina to study folic acid use among mothers and found that only 22% of mothers with a previous NTD-affected pregnancy reported using folic acid. This study showed a significant difference in recurrence rate among high-risk women with and without high-dose folic acid supplementation: 0.4% and 8.5%, respectively [12]. The National Birth Defects Prevention Study data from the US showed that 35% of mothers who had an NTD-affected pregnancy in the past reported taking high-dose folic acid as a recurrence prevention measure [13].

Studies on the prevalence of high-dose folic acid use for prevention of recurrent NTDs in low- and middle-income countries are largely lacking. Ethiopia, for example, has a high prevalence of NTDs and stillbirths associated with NTDs, as identified by data across various regions of the country [14–16]. In the northern area of Ethiopia, Tigray has been shown to have an even higher incidence rate of 13.1/1000 births, with 23% being live births [14]. In a report from a large referral hospital in the capital city of Ethiopia, 177 cases of NTDs were identified out of 28,961 deliveries, giving an overall NTD prevalence of 6.1/1,000 [16]. Each of these mothers who had a pregnancy affected by NTDs in the past has a high risk of an NTD in a subsequent pregnancy and should be prescribed 4-5 mg of folic acid per day to prevent a recurrent NTD. The current study aimed to understand the 5 mg/day folic acid prescription practices (the standard in Ethiopia for high-risk prevention) for mothers who had a baby with spina bifida and who received care at a large urban tertiary care hospital that serves as a Center of Excellence in Spina Bifida and Hydrocephalus Care in Ethiopia.

2. Methods

Data were extracted from a Research Electronic Data Capture (REDCap) database containing electronic medical records for spina bifida and hydrocephalus care at one urban teaching tertiary care hospital in Addis Ababa, Ethiopia, in June 2022. This database was made available at the tertiary care hospital with the help of ReachAnother Foundation, a non-profit organization that enhances spina bifida and hydrocephalus treatment, prevention, and aftercare in Ethiopia [17]. Neurosurgeons, surgical residents, and general practitioners at the hospital have contributed data to the REDCap database since 2019. At the end of each patient encounter at this hospital, a general practitioner sat with the mother and her medical record to fill in the database with information about the child's encounter. If, due to time constraints or technology issues, the database could not be filled out on the spot, then the data was retroactively entered. If the mother was reported to have a folic acid prescription, then this indicated that a nurse, the Spina Bifida Care Coordinator, or a general

practitioner spoke to the mother about the benefits of folic acid and provided a prescription.

The analytic sample for the current study was limited to babies born between January 2019 and June 2022 with a spina bifida (myelomeningocele or meningocele) diagnosis logged during at least one patient encounter at the hospital. At each patient encounter, mothers at the study hospital are expected to receive counseling about the benefits of folic acid supplements for spina bifida recurrence prevention and a prescription for 120 pills containing 5 mg of folic acid, which would fulfill the recommended dose of folic acid for approximately 4 months. The 5 mg dosage is used instead of 4 mg due to the wide availability in the Ethiopian market. The mother can return to fill additional prescriptions.

The primary outcome measure was the number of folic acid prescriptions that each mother received following a patient encounter, where the child received care preceding or following a spina bifida closure surgery. The frequency of mothers who received 0, 1, or 2–3 folic acid prescriptions throughout the duration of the study period was calculated. Findings were also presented by the birth year of the infant with spina bifida. REDCap data collected basic demographic factors for each child and their mother. Demographic variables, including infant sex and maternal residence, were available for descriptive analysis. Regions of maternal residence for five patients or fewer were aggregated into an "Other Region" category for patient privacy purposes. Chi square tests were performed to determine whether the percentage of mothers receiving a folic acid prescription significantly differed according to these demographic characteristics.

3. Results

From January 2019 to June 2022, 500 children were documented in the REDCap database with a diagnosis of spina bifida (myelomeningocele or meningocele) identified during at least one patient encounter at the urban tertiary-care hospital that served as the study site. Among these 500 children, 281 (56.2%) were male, 217 (43.4%) were female, and two (0.4%) did not have sex information reported. The majority of the mothers of these children resided in the capital city of Addis Ababa, followed by the Oromia region. Regarding year of birth, 73 babies (14.6%) were born in 2019, 143 (28.6%) were born in 2020, 214 (42.8%) were born in 2021, and 70 (14%) were born between January and June 2022 (Table 1).

Table 1
Demographic distribution of Mother-Baby Pairs ($N = 500$)

Characteristic	Frequency	Percent
Child's Sex[1]		
Male	281	56.2%
Female	217	43.4%
Region of Maternal Residence[1]		
Addis Ababa	198	39.8%
Amhara	76	15.3%
Oromia	182	36.5%
SNNPR[2]	23	4.6%
Other Region[3]	19	3.8%
Year of Birth of the Infant		
2019	73	14.6%
2020	143	28.6%
2021	214	42.8%
2022[4]	70	14.0%

[1]Does not total to 500 due to missing data. [2]Southern Nations, Nationalities, and Peoples' Region. [3]Regions including five or fewer patients, which included Afar, Benishangul-Gumuz, Dire Dawa, Gambela, Harari, and Somali. [4]January-June 2022.

Out of a total of 500 mothers with infants who had spina bifida, 340 (68.0%) received a 5 mg/day folic acid tablet prescription for 120 days when they were at the hospital to receive clinical care for their child. Of these 340 mothers, 97% ($n = 331$) received their prescription at their child's first or second patient encounter documented at the hospital, which are typically one week and one month, respectively, after discharge from the child's first surgery.

The majority of mothers (94%) who received a folic acid prescription had documentation of only one prescription (i.e., 120 tablets) for the study duration, sufficient for only approximately four months. The receipt of a folic acid prescription did not differ between mothers with a female child (65.4%) and mothers with a male (70.0%) ($p = 0.27$); however, the receipt of folic acid prescriptions significantly varied based on the mother's region of residence. For example, 75.1% of mothers residing in the capital city of Addis Ababa received at least one folic acid prescription, whereas this percentage was 61.5% for the region of Oromia and 65.8% for the region of Amhara ($p = 0.002$). The place of residence of the mother likely contributed to the prescription pattern as mothers from the capital city are more likely to be educated and therefore adherent to follow-up. Additionally, mothers from the other regions would need to travel a long distance to come for follow-up visits post-surgery, which in turn would lead to lower rate of folic acid prescription in the group.

The proportion of mothers that received folic acid prescriptions at least once varied by the child's year of birth (2019:75%; 2020:92%; 2021:46%; 2022:79%) ($p < 0.001$).

4. Discussion

This study was one of the few descriptive epidemiological studies to examine recurrence prevention practice in a low- and middle-income country (LMIC) setting, especially one with a documented high prevalence of NTDs. Results showed that 68% of mothers with children with a spina bifida diagnosis received a 5 mg/day folic acid prescription for recurrence prevention at the study hospital, which also serves as a Center of Excellence in Spina Bifida and Hydrocephalus Care in Ethiopia. No notable differences were observed in prescription practices according to the child's sex. Some variation was seen in prescription practices according to the family's region of residence; however, most regions were only sparsely represented. Prescription practices did vary across birth years. A stark drop in reported prescriptions was seen in 2021, which was likely attributable to the COVID-19 pandemic, and the receipt of prescriptions rose again in 2022. Among the mothers who received folic acid prescriptions, most received it within their child's first or second patient encounter, which is positive; however, 94% of the mothers who received folic acid prescriptions received only one prescription, which provides only a 120-day supply.

That the majority of high-risk mothers at this tertiary care center received 5 mg folic acid prescriptions is laudable and a testament to the organization of the neurosurgeons, general practitioners, nurses, and spina bifida care coordinators [17]. It is also evidence of the tremendous efforts of ReachAnother Foundation in their partnership with this tertiary care center to optimize the prevention of spina bifida [17]. This prioritization of recurrence prevention should be emulated worldwide, but efforts can be improved by providing the folic acid tablets to mothers at the appointment rather than just the prescription. Resources for healthcare professionals to intermittently follow up with mothers to provide timely refills and counseling for adherence would also be beneficial.

This study was subject to several limitations. It measured the administration of folic acid prescriptions, but this does not directly capture how many prescriptions were filled or adherence to the prescription. The study could not evaluate in detail the barriers to filling and taking the supplements prior to the mother's next conception. This study also captured only mothers of children who presented to this tertiary care center and received care. It did not capture the folic acid prescription access of mothers who received elective terminations, had non-live birth pregnancy outcomes, or did not have access to neurosurgical care from this center. Additionally, information on demographic factors among patients in the REDCap database were limited, as the general practitioners were challenged with balancing robust data collection with a high clinical patient load. While the database was designed to follow the child across multiple encounters, it did not allow siblings to be linked, so subsequent pregnancy outcomes could not be examined in relation to folic acid prescription practices following a mother's prior pregnancy. Despite these limitations, this is the first study to emerge from an important new source of data about children with spina bifida in Ethiopia. The key message holds true: this Center of Excellence in Spina Bifida and Hydrocephalus Care in Ethiopia is taking foundational steps in recurrence prevention, and more resources will support implementation.

Further research is needed to examine factors that promote the continuous supply of high-dose folic acid to high-risk women and their adherence to this intervention in Ethiopia. The REDCap database used in this study can be expanded upon to collect data on the awareness of mothers about high-dose folic acid as a prevention strategy when there is a history of NTD-affected pregnancy and additional demographic factors. The database can also help identify factors associated with low compliance among mothers and advocate for measures that promote the success of recurrence prevention. This REDCap database is being implemented at all eight Centers of Excellence across Ethiopia, so there is also potential to explore these questions across other Ethiopian regions [17].

Flood et al. suggested a list of recurrence prevention activities that can be undertaken with minimal staff requirements and may be applicable to hospital settings with limited resources toward recurrence prevention [10]. Some of these activities can be tailored to the Ethiopian context: (a) Educate mothers about recurrence risk and prevention and provide 5 mg/day folic acid supplement pills if they are planning a pregnancy in the near future; (b) Involve patient support groups to deliver educational messages about recurrence prevention; (c) Include health

extension workers specifically targeting high-risk mothers in recurrence prevention programs; (d) Conduct outreach to high-risk women with information pamphlets and mobile phone messages on recurrence prevention; and (e) Reach high-risk mothers in a variety of clinical settings (e.g., obstetrics and gynecology, spina bifida clinic, primary healthcare centers, pediatric clinics). South Carolina in the US, which had a high burden of NTDs, has shown significant success in preventing recurrence of NTDs through genetic counseling and public awareness campaigns promoting folic acid supplementation [18, 19]. Future intervention research is warranted to understand whether this approach from South Carolina can serve as a model for tertiary care hospitals in Ethiopia.

The recommended folic acid prescription practice for recurrence prevention needs to be strengthened so that all mothers benefit from this intervention. Recurrence prevention programs should be integrated into the care strategy beyond tertiary care hospitals so mothers can receive needed high-dose folic acid from other departments (e.g., gynecologists and obstetricians, primary health care settings). Additionally, Ethiopia's health extension workers can deliver 5 mg/day folic acid prescriptions to help mothers maintain a continuous supply of folic acid directly at their homes, mitigating the need to travel to urban tertiary care hospitals, which may be prohibitive for many women. Beyond the prescription practice, prioritizing sustained funds to provide high-risk women with free folic acid tablets can favor high compliance and uptake of this important recurrence prevention strategy, overcoming disparities related to folic acid access and affordability. Concurrent with efforts to reduce loss-to-follow-up among children with spina bifida, NTD recurrence prevention practices should be a consistent topic of conversation between healthcare providers and mothers.

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Conflict of interest

The authors have no financial relationships relevant to this article to disclose.

Ethical considerations

Institutional review board approval was received and a waiver of informed consent was granted to assess an electronic record available at the tertiary care center.

Data availability statement

This is clinical data, and a de-identified dataset can be accessed per request of the corresponding author.

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