Impact of Wheat Flour Folic Acid Fortification on Neural Tube Defects in Three Cities in Peru

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Objective: The purpose of this study was to assess the impact of fortification of wheat flour with folic acid on the prevalence of neural tube defects (NTDs) in three hospitals of the three natural regions of Peru by reducing anencephaly, spina bifida or encephalocele.

Methods: In 2012, a retrospective descriptive study of NTD prevalence in three public hospitals was conducted. The data corresponded to two periods: before (2001-2005) and after (2006-2010) implementing mandatory fortification of wheat flour with folic acid and other micronutrients in August 2005. Prevalence was calculated by dividing the total number of NTDs identified in the three hospitals by the total number of live newborns in the three hospitals (91.413) in 2001-2010. The 95% CI was calculated for NTD prevalence with the Poisson Test.

Results: A total of 101 newborns were found with an NTD, with mean gestational age of 37.7 weeks and mean weight of 2,808.6 grams. The prevalence of NTDs in the pre-fortification period was 12.1 per 10,000 live births and 10.1 per 10,000 live births in the post-fortification period. Pre- and post-NTD prevalences (per 10,000 live births) were 16.6 and 15.9 in Ayacucho, 12.3 and 10.1 in Tacna and 8.0 and 4.9 in Iquitos. Only the prevalence of spina bifida had a statistically significant reduction of 3.7 per 10,000 live births (p <0.05).

Conclusions: The implementation of wheat flour fortification with folic acid helped reduce the prevalence of NTDs in 2 per 10,000 NB, suggesting a positive impact of the intervention in the three study hospitals.

Introduction

In Latin American countries where infant mortality has declined to below 50 per 1,000 live births, congenital anomalies are the second or third cause of infant mortality, and therefore are a significant public health problem.[1] In Costa Rica, for example, neural tube defects (NTDs) are the second-leading cause of infant mortality.[2] Although in Peru infant mortality has been declined in recent years to 17 per 1000 live births, there are no specific data on morbidity and mortality by NTDs. NTDs are incurable birth defects that occur between the second and fifth weeks of embryonic development.[3,4] NTDs, such as anencephaly, spina bifida, encephalocele and others represent 85% of all central nervous system malformations.[5,6,7] Spina bifida occurs in 50% of cases of NTDs, anencephaly in 40% and encephalocele in 10%.[8] Anencephaly is fatal at or within a few hours of birth; spina bifida causes children to be paraplegic, develop hydrocephalus and suffer gastrointestinal and genitourinary problems. Since NTDs are incurable, prevention is the best option.

Although many factors (e.g. environmental, nutritional, genetic and ethnic) influence the occurrence of an NTD, the effect of other factors remains unknown. There is an increased need of folate during embryogenesis, growth and fetal development in the first months of gestation for the synthesis of nucleic acids and proteins.[9,10] As NTDs are associated with maternal folic acid insufficiency during pregnancy, strategies using folates attempt to prevent micronutrient deficiencies in the population and help prevent birth defects such as NTDs.[11,12,13] Regarding folic acid, Peru issued a law to fortify wheat flour with folic acid and other micronutrients. Under the initiative of Peruvian National Institutes of Health and the Ministry of Health, the government of Peru promoted Law 28314. It then approved the mandatory fortification of wheat flour with 1.2 mg of folic acid, iron and other micronutrients per kilogram. On August 4, 2005 regulations were formalized, with expected fortification implementation to be at 100% in one year.

Unlike other countries, where studies were conducted prior to the fortification of wheat flour to obtain a folic acid baseline, this did not occur in Peru. Without a folic acid baseline, direct quantification of the impact of the fortification on NTDs was not possible. As a way to measure the impact of the intervention in Peru, studies measuring the prevalence of NTDs before and after fortification were conducted in the National Maternal and Perinatal Institute in the Peruvian capital, Lima.[14,15] Although those studies demonstrated the effectiveness of wheat flour with folic acid fortification in Lima, no other studies were done in the interior of the country in order to measure its impact.

On the basis that fortification of wheat flour with folic acid would reduce the risk of occurrence of births with NTDs, this study evaluated the impact of Peru's fortification program on NTDs in three main hospitals in three cities of the natural regions of Peru.[16]

Table No. 1. Characteristics of mothers of babies with neural tube defects in three cities of Peru; 2001-2010

Characteristics	Nº	%
Maternal age		
Adolescent	16	15.8
Adult	60	59.4
Not reported	25	24.8
Education		
No education	1	1
Primary	19	18.8
Secondary	42	41.6
College	9	8.9
Not reported	30	29.7
Civil status		
Single	9	8.9
Married	12	11.9
Cohabitation	52	51.5
Not reported	28	27.7
Mother in stable relationship		
No	9	8.9
Yes	64	63.4
Not reported	28	27.7
Mother's occupation		
House wife	64	63.4
Working	11	10.9
Student	2	2
Not reported	24	23.8
Prenatal care		
No prenatal care	12	11.9
Prenatal care	43	42.6
Not reported	46	45.5
Four or more prenatal visits		
No	7	6.9
Yes	36	35.6
Not reported	58	57.4

Methods

A retrospective descriptive study of NTD prevalence in three hospitals from selected representatives' cities of natural regions of Peru was performed from July to December 2012. The prevalence of NTDs during two different periods (before implementation of Law 28314, and after) were calculated, with 2001-2005 representing the period before and 2006-2010 representing the period after fortification. Hospitals from which the information was obtained corresponded to the public sector (Ministry of Health), with higher birth care coverage in the cities of Ayacucho in the Ayacucho Region (mountain range at 2,761 m.), Iquitos in the Loreto Region (jungle) and in the Tacna Region of Tacna (coast). Regions were selected for convenience.

The sample population was 91,413 live births, which corresponded to the total number of newborns in the three selected hospitals in the ten-year study period who met the requirement of complete medical history and diagnosis of an NTD. Characteristics of mothers of live births with NTDs in each hospital are presented in Table 1. Live births, by hospital, during the ten- year period are presented in Table 4.

While the objective was the measurement of the prevalence of NTDs, it was decided to review all medical records. We did not include stillbirths, abortions or pregnancy terminations for congenital anomalies.

Techniques and Instruments

To collect the data for live births with NTDs an ad hoc structured form was used. The data collected on the mother (?) included age, education, occupation, family background, folic acid supplementation during pregnancy and prenatal care; the data collected on the newborn included gestational age at birth, sex, weight, Apgar and type of NTD.

For the validity of the instrument for data collection, the opinion of five experts was obtained. A Kappa test was used to assess agreement for data collection between evaluators, and a high concordance was found.

Subsequently, health professionals from selected hospitals were

instructed to obtain data from medical records. The list of NTD cases from the Statistical Office of each hospital was requested. The medical records of the corresponding live newborns during the study period were requested to verify the diagnosis. In instances where a list was not available, other documents and the medical records were requested.

Ethical considerations

The study was evaluated and approved by the Research Council of the National University of San Marcos. An authorization from the Directorate General and the Ethics Committee of the hospitals where the study was conducted was obtained. A code was allocated to each of the cases included in the database. The first and last names of the newborn and the mother were not recorded.

Statistical analysis

An exploratory analysis of quantitative variables to assess the normality of the data was performed finding a normal distribution. The qualitative variables were presented as frequencies, percentages, averages, standard deviations and confidence intervals through the Poisson test. The overall prevalence of NTDs was calculated before and after fortification, considering newborns with any NTD among total newborns in the period of observation. NTD prevalence was calculated per hospital for the three hospitals and according to the type of NTD. To evaluate whether the observed reduction was significant, the Z test was used (a difference in proportions during the pre-and post-fortification periods, and $p < 0.05$ was considered statistically significant. 95% CIs were calculated with the Poisson Test for all prevalences.

Results

The overall average age of the mothers was 24.9 years with standard deviation ± 6.3 years, ranging from 14 to 40 years. Other characteristics of mothers of live births with NTDs in the three hospitals are presented in Table 1, but approximately 25% of those data had not been recorded in the hospitals' medical history. It was found that the average gestational age was 37.7 weeks and the average weight 2.81 kilograms, both before and after fortification. Live births before and after fortification scored between 1 and 9 on the one-minute Apgar; Apgar scores at 5 minutes fluctuated between 1 and 10. Scores of 7 and above are generally normal, 4 to 6 fairly low, and 3 and below generally regarded as critically low. A low score on the one-minute test may show that the neonate requires medical attention.

Overall NTD prevalence for the three hospitals saw a decrease of 2 per 10,000 LB during the post-fortification period. One city of study, Ayacucho, had a higher prevalence of NTDs during the pre-fortification period with 16.6 per 10,000 LB, which reduced by 0.7 ($p > 0.05$) to 15.9 per 10,000 LB during the post-fortification period. Likewise in Iquitos, a 3-per-10,000 LB reduction in the prevalence between the two periods of study was found ($p > 0.05$). Other results for the pre- and post-fortification periods in other cities are presented in Table 2.

Comparing prevalence by type of NTD between the two periods, it was found that post-fortification prevalence of spina bifida reached 5.1 per 10,000 LB, representing a reduction by 3.7 per 10,000 LB. Prevalences of anencephaly and encephalocele were not reduced. Other results related to type of NTD for the pre- and post-fortification periods are presented in Table 3.

The number of births in all hospitals of study is presented in Table 4.Given the above strengths and limitations, the implications

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of this study's findings are threefold and the authors offer a few recommendations of recourse such as filling data gaps and securing improved working conditions for immigrants, racialized persons and women in order to minimize the risk of MSDs. First, government financial support programs should be considered in order ensure adequate surveillance and data collection of musculoskeletal injuries that is stratified by gender, ethnicity and immigrant status. Secondly, the findings could warrant policy changes that would prioritize occupational health, allow for greater recognition of immigrant skills and experiences and introduce employment models that would in turn allow for increased flexibility to fit the needs of women workers. Finally, the issues presented should also be on the agenda of global public health research, as ignoring them will lead to the possibility of diminished occupational health of workers.

Discussion

Studies in Lima showed reduction of NTDs in the National Maternal Perinatal Institute of Lima after implementation of the fortification of wheat flour Law 28314 in Peru, but not in cities located on the coast, mountains and jungle of Peru, a gap which this study attempts to redress.[14,15,17] This difference may be due to a lack of uniformity in data collection in some hospitals or omission by coders and diagnoses made in-hospital and not included on discharge records. In addition, there is a lack of neonatologists, whose knowledge is needed for a good diagnosis. Therefore, we suggest that hospitals without neonatologists have guides that include photographs of various forms of NTDs to facilitate diagnosis by other health professionals.

Overall results show a decrease in the prevalence of NTDs by 2.0 per 10,000 LB during the pre and- post-fortification periods ($p = 0.184$). While these results are not statistically significant, our results

Table No. 2. Distribution of neural tube defects prevalence in three cities of Peru; 2001-2010

Region	Pre fortification					Post fortification					P value
	Nº NTD	Nº LB	Prevalence per 10000 LB	CI 95%		Nº NTD	Nº LB	Prevalence per 10000 LB	CI 95%		
Ayacucho	20	12014	16.6	(10.2;	25.7)	24	15085	15.9	(10.2;	23.7)	0.441
Tacna	20	16204	12.3	(7.5;	19.1)	18	17858	10.1	(6.0;	15.9)	0.267
Loreto	11	13833	8.0	(4.0;	14.2)	8	16419	4.9	(2.1;	9.6)	0.148
Total	51	42051	12.1	(9.0;	15.9)	50	49362	10.1	(7.5;	13.4)	0.184

Table No. 3. Distribution of neural tube defects by type in three cities of Peru; 2001-2010

NTD type	Pre fortification				Post fortification				P Value
	Nº NTD	Prevalence per 10,000 LB	CI 95%		Nº NTD	Prevalence per 10,000 LB	CI 95%		
Anencephaly	7	1,7	(0,4;	2,9)	16	3,2	(1,7;	4,8)	0,938
Encephalocele	7	1,7	(0,4;	2,9)	9	1,8	(0,6;	3,0)	0,572
Spina bifida	37	8,8	(6,0;	11,6)	25	5,1	(0,6;	3,0)	0,017

Table 4. Distribution of births in three cities of Peru*

Años	Tacna	Loreto	Ayacucho	Total
2001	2693	1974	2072	6739
2002	3185	2750	2194	8129
2003	3198	3198	2564	8960
2004	3449	3323	2260	9032
2005	3679	2588	2924	9191
2006	3526	3181	3153	9860
2007	3612	3440	2917	9969
2008	3532	2852	2869	9253
2009	3673	3511	3084	10268
2010	3515	3435	3062	10012

* Total of newborns in hospital

are consistent with those reported by Sanabria et al. in the National Maternal and Perinatal Institute in Peru, which indicate a significant decrease of NTDs by 4.9 per 10 000 LB during the two periods.[14,15] As we know, there are unknown causes of NTDs that could possibly have led to these nonsignificant changes.

There is an impact of wheat flour fortification with folic acid in different countries. Brazil showed a reduction by 2.1 per 10,000 LB.[18] Chile reported a 31% drop in the prevalence of NTDs after wheat flour fortification started with folic acid in the year 2000.[19,20,21] Argentina also saw a significant reduction in mortality from neural tube defects by 67.8% for spina bifida and 56% for anencephaly.[22] Costa Rica not only fortified wheat flour but also corn, rice and milk, and showed a reduction in NTDs by 39% in the third year of fortification, an early fortification effect.[23] Having observed no greater positive impact in Peru with the fortification recommended by Law 28314, authorities should think about folic acid fortification of other foods.

While the highest prevalence of NTDs was reported in Tacna,

on the coast, results from both pre- and post-fortification periods differ with those reported by Saldarriaga et al., who postulated a possible association between the occurrence of NTDs and living at higher altitudes of around 2,000 meters.[24] Such geography is seen in Ayacucho, located on the mountain range at 2,746 meters above sea level. In this context, Cook et al. reported a lower prevalence of folate deficiency in non-pregnant women of childbearing age, a situation attributed to the adequate intake of folate by eating foods that provide folic acid, such as ceviche, which is not consumed as much in the mountain range in Ayacucho.[25] It is noteworthy that in Loreto (jungle) and Tacna (coast), reduction of NTD prevalence was higher than in Ayacucho (mountain). This could be due to a lower intake of products derived from wheat flour in Ayacucho, as the city is the capital of one of the poorest regions of Peru. It could also be that in Ayacucho wheat flour has had an ineffective fortification level of micronutrients. Even though there is a national fortification mandate, monitoring and regulation of the mandate is not necessarily so enforced in other cities of the country as they are in the capital Lima. This situation may explain differences between findings in Lima, Iquitos, Tacna and Ayacucho.

By analyzing the NTD reduction according to type, it was observed in this study that there was a significant reduction in spina bifida ($p = 0.017$), but not encephalocele or anencephaly. Our results were consistent with those reported in Costa Rica, Chile and Canada.[22,26,27] However, this was not observed in the study of Sanabria et al., where it was found that the prevalence for anencephaly decreased, going from 5.1 to 1.9 per 10 000 LB (95% CI 1.0, 2.8), post-fortification; in his study the decrease for spina bifida and encephalocele were not statistically significant.[15] We don't have any explanations for doubling anencephaly cases in our study, as reasons for the increased risk of anencephaly among Hispanic mothers are not well understood.[28] Our results on prevalence of encephalocele are different from other studies in which reduction was observed in spina bifida, anencephaly and encephalocele.[22,27,29] An explanation is required for the non-reduction of the prevalence of encephalocele as well.

Although some medical records with NTDs were not located during the study, the expected reduction of neural tube defects was not evident; this limitation could be related to poor information systems, registration and storage of medical records, as well as a smaller number of diagnoses of congenital malformations due to a lack of specialists in the country. It is known that there are limitations in Peru for meeting the Classification of Diseases ICD-10 of the World Health Organization, such as various forms of underreporting or a lack of neonatologists who are needed for a good diagnosis.[28] It is likely that further observation by health professionals in the post-intervention period could have contributed to a greater overall decrease in the prevalence anencephaly, encephalocele, spina bifida and the other types of NTDs.

Lower NTD prevalence can be attributed to regions where wheat flour product consumption is high. Article 14 of the regulations of Law No. 28314, which ordered the fortification of wheat flour with micronutrients, states: "the National Center for Food and Nutrition conduct studies to determine the availability, access and consumption wheat flour and its derivatives as well as for measuring the impact of the fortification program."[17] As this means nutritional surveillance, improved logging also involves the implementation of an epidemiological surveillance system for NTDs nationwide, which already exists in Costa Rica, Nicaragua, Chile and other countries. Monitoring of compliance with the fortification of wheat flour with folic acid inside the country by the National Center for Food and Nutrition in production centers is also important. It will help to significantly decrease the overall prevalence of all forms of NTDs in Peru, since the great benefits of the use of folic acid can lead to reducing the incidence up to 72% of NTDs according to Kramer.[30]

In conclusion, after the implementation of the fortification of wheat flour in Peru in time and places of study, the overall reduced prevalence of NTDs was statistically insignificant at 2 per 10,000 RN ($p > 0.05$), but the reduced prevalence of spina bifida was significant at 3.7 per 10,000 LB ($p < 0.05$).

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