ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2025;96(1):74-82
DOI: 10.32641/andespediatr.v96i1.5327

ORIGINAL ARTICLE

Clinical and sociodemographic aspects of patients with Myelomeningocele

Aspectos clínicos y sociodemográficos de pacientes portadores de Mielomeningocele

José Arroyo[a], Danitza Campos[a], Pablo Alarcón[a], José Suazo[b], Luis Aldana[c], Andrea Solervicens[d], Pablo Vejar[e], Gustavo Parada[f], Rosa Pardo[a,g]

[a]Sección Genética, Hospital Clínico Universidad de Chile. Santiago. Chile.
[b]Instituto de Investigación en Ciencias Odontológicas, Facultad de Odontología, Universidad de Chile. Santiago, Chile.
[c]Instituto Teletón Concepción. Concepción, Chile.
[d]Instituto Teletón Valdivia. Valdivia, Chile.
[e]Instituto Teletón Iquique. Iquique, Chile.
[f]Instituto Teletón Antofagasta. Antofagasta, Chile.
[g]Corporación Espina Bífida Chile (CORPEB).

Received: Jun 21, 2024; Approved: October 9, 2024

What do we know about the subject matter of this study?

In Chile, about 100 children are born with myelomeningocele (MMC) per year as a result of the public health strategy of fortifying wheat flour with folic acid initiated by the Ministry of Health in January 2000. However, there are no Chilean series describing both the sociodemographic and clinical characteristics of patients with MMC and their families to guide new interventions in order to improve their quality of life.

What does this study contribute to what is already known?

This research shows that in the cohort studied there is a low rate of prenatal diagnosis (63.5%), in utero repair of MMC (15%), and use of folic acid supplementation (12%), while the other parameters evaluated showed results very similar to those reported in the international literature.

Abstract

Myelomeningocele (MMC) is one of the most common congenital anomalies in humans, with a high morbidity and mortality burden. Its causes are multifactorial, the most prominent factor being maternal folate deficiency. In Chile, the prevalence is 4.4 per 10,000 births and there are no published data on the clinical and sociodemographic characteristics of people with MMC in the country. **Objective:** To describe clinical and sociodemographic aspects in a sample of patients with MMC. **Patients and Method:** Descriptive cross-sectional study of a sample of 200 Chilean patients with MMC and their parents, who were administered two surveys: one on perinatal sociodemographic data, and another on health data of the participant, including level of the lesion, time of diagnosis, ability to

Keywords:
Meningomyelocele;
Spinal Dysraphism;
Hydrocephalus;
Folic Acid;
Chile

Correspondence:
Rosa Pardo
rpardo@hcuch.cl

Edited by:
Carolina Heresi Venegas

How to cite this article: Andes pediatr. 2025;96(1):74-82. DOI: 10.32641/andespediatr.v96i1.5327

walk, and complications. **Results**: Most of the patients with MMC were female (55%), had the lesion under T12 (83%), were diagnosed prenatally (63.5%), and were able to walk (71.3%), although with assistive devices. Only 15% had *in utero* MMC repair. The most frequent complications associated with MMC were neurogenic bladder (74%), hydrocephalus (74%), and Chiari II malformation (36%). Only 12% of mothers reported using folic acid as a preconception supplement. **Conclusions**: The data presented provide information on the sociodemographic and clinical conditions of Chilean patients with MMC and their families. It is expected that studies like this one and other prospective ones with larger samples will contribute to the design of health strategies for the comprehensive and timely management of patients with MMC in Chile.

Introduction

Spina bifida (SB) is the most common and complex congenital defect of the central nervous system that is compatible with long-term survival[1,2,3]. SB, together with anencephaly and encephalocele, is part of the neural tube defects (NTDs), which are congenital anomalies preventable in 50% to 70% of cases through supplementation and fortification with folic acid[4].

About 80 to 90% of SB cases correspond to myelomeningocele (MMC)[1], an open spinal dysraphism produced by failures in the neurulation process, which affects the fusion of the caudal region of the neural tube. MMC can manifest at any level of the spine, exposing the spinal cord and meninx due to lack of bone, soft tissue, and skin. This exposure commonly causes neurological damage, weakness, and/or deformity of the lower extremities, sensory loss, and compromised bladder and bowel function, among others[3].

The causes of NTDs are mostly multifactorial, in a not fully understood interaction of both environmental and genetic factors that are under extensive study, with only 10% of all NTD cases being part of a genetic syndrome (trisomy 13, trisomy 18, or triploidy)[2]. Among the genetic factors, the risk of recurrence of NTD after the birth of an affected child has been reported to be higher than that of the general population, with an estimated recurrence risk of 2-5%[3]. Twin studies have suggested a higher concordance for NTDs between twins of the same sex (monozygotic and dizygotic) compared with twins of the opposite sex (dizygotic only). In addition, there are notorious differences according to fetal sex, with anencephaly being more prevalent in females than in males, a relationship that does not occur in the case of spina bifida[4]. Possible epigenetic relationships and ethnic differences in the prevalence of NTDs have also been observed, being higher in Caucasian and Hispanic populations[5,6]. As for maternal environmental risk factors, obesity, diabetes, and the use of drugs (such as valproic acid, carbamazepine, trimethoprim, and methotrexate, among others) have been described[7], but the most widely studied risk factor with the most evidence is folate deficiency[8]. This association allowed the development of public health strategies to establish fortification and/or supplementation with folic acid for women of reproductive age in many countries of the world and, since 2022, fortification has been mandatory in 68 countries[9].

Worldwide, the incidence of SB varies between 4.19 and 8.67 cases per 10,000 births[10,11]. In Chile, the prevalence is 4.4 cases per 10,000 births given a 51% reduction of cases following the implementation of the wheat flour fortification program with folic acid in January 2000 by the Ministry of Health[12], which is a highly cost-effective strategy[13].

It is estimated that in Chile about 100 children are born with SB per year[14]. Before the first half of the 20th century, international follow-up studies showed a case fatality rate of close to 90% for individuals with MMC, with most deaths occurring during infancy. However, advances in medical care and surgical interventions have significantly improved their survival rate, so that there are reports during the second decade of the 21st century that show case-fatality rates between 2.2% and 37% of children with MMC before adulthood, depending on the socioeconomic level of the country, with the highest survival rate reported in the Netherlands and the lowest in Uganda[15]. In Chile, there are no published data on the survival of children with MMC.

Multiple factors have contributed to the decrease in the case fatality rate such as the development of surgical repair techniques (pre- and postnatal), intermittent bladder catheterization, folic acid fortification (associated with lower and less extensive defects), and better perinatal care, among others. Although hydrocephalus and Arnold-Chiari type 2 malformation (CM-II) are still frequent complications in children with MMC, a significant decrease of these has been evidenced with prenatal correction of the defect, reducing the need for ventriculoperitoneal (VP) shunt placement[16]. However, children with MMCs still have

a high morbidity rate; some individuals will never develop gait or adequate sphincter control[17]. In addition, 20-25% have some type of cognitive impairment, most commonly in the domains of attention, mobility, perception, language, arithmetic, and memory[18]. These conditions are associated with increased healthcare costs for each family, which can deteriorate the psychosocial and economic conditions of affected families.

All this reflects the important need for knowledge of the health and socioeconomic conditions and characteristics of the population affected by SB in the country, in order to better prepare the health system for its adequate treatment and follow-up and to favor the best quality of life conditions for this group of people. The objective of this study was to describe clinical and sociodemographic characteristics in a sample of Chilean people with MMC.

Patients and Method

This is a study carried out by a research team from the Genetics Section of the *Hospital Clínico Universidad de Chile* and *Fundación Teletón Chile*. The sample analyzed is part of a larger ongoing study, which seeks to analyze genetic variants called "Epigenetics and spina bifida, variants in chromatin organization genes are associated with increased risk for this pathology".

The sample is composed of 200 trios (children with MMC and their parents) of Chilean individuals, who participated voluntarily and were recruited through an invitation to families linked to *Corporación Espina Bífida Chile* (CORPSB), *Teletón Chile* (Santiago, Valparaíso, Antofagasta, Iquique, Concepción, and Valdivia), as well as an open call to those interested in participating through social networks.

The inclusion criteria were: 1) Chilean families with a child (proband) diagnosed with MMC, 2) that the MMC is an isolated congenital defect, and 3) availability of participation of both parents.

Exclusion criteria used were: 1) that any member of the trio expressed at some point their intention to leave the study after having been recruited.

An interview was conducted by one of the co-investigators or a nurse in which two surveys were filled out, one with perinatal sociodemographic data applied to the parents, and another survey that collected clinical health data of the proband. If the parents did not know any of the required clinical data and the proband was being followed by one of the *Teletón* institutes, the *Teletón* co-investigators could access the proband's clinical record to complete these data, as stated in the informed consent and assent forms.

Both surveys were generated by the Latin American and the Caribbean Neural Tube Defects Network and had been previously validated in the Chilean population (2010) with members of the CORPSB.

The data obtained were tabulated in Excel spreadsheets to then apply descriptive statistical analysis of the sample, using medians, means, modes, ranges, and percentages to achieve the characterization of the sample.

This research protocol was reviewed and authorized by the Scientific Ethics Committees of the *Hospital Clínico Universidad de Chile* and *Teletón Chile*.

Results

Demographics

The 200 participating families reported that during the first three months of pregnancy, they lived mainly in the Metropolitan Region (40.5%) and in the South-Central Macrozone (24.5%) (Table 1).

55.5% (111/200) of children with MMC were female and the mean age at the time of the survey was 9 years and 7 months (2 months - 29 years). The minority of mothers were first-time mothers 37% (74/200) and only 2% (4/200) had a history of previous children with NTDs (three with SB and one with anencephaly).

The median maternal age at pregnancy was 29 years (14 years - 43 years), 11 (5.5%) were teenage mothers, and 10 (5%) mothers were 40 years or older.

Prenatal diagnosis of MMC was made in 63.5% of the cases (128/200) and 30 (15%) children with MMC underwent surgery to repair the defect *in utero*. Delivery was by cesarean section in 82.5% of the cases, 19% being preterm. The mean birth weight was 3074 grams (range 690 gr - 4980 gr), with 16% (32/200) having birth weight ≤ 2500 grams. 83% (166/200) of the children with MMC had a low lesion (L1 downwards), and in 20 cases (10%) the exact level of the origin of the lesion could not be determined.

Motor development and orthotics

Regarding motor development milestones, 71.3% (124/174) of the patients older than 18 months achieved ambulation (Table 2), most of them needed some type of assistive device for walking (62.6%; 109/174), and the most used were ankle-foot orthoses (131 ankle-foot orthoses, 44 walkers, 19 crutches, and 11 forearm crutches were indicated in total).

Associated complications

Associated complications were common. Neurogenic bladder was present in 74% (148/200) of cases, CM-II in 36% (72/200), hydrocephalus in 74%

(148/200), tethered cord in 35% (70/200), clubfoot in 30% (60/200), and 64% (128/200) required a VP shunt at some point.

Other Interventions

126 (63%) children with MMC underwent clean intermittent catheterization (CIC) and, when considering only patients older than 19 years of age, 74% (20/27) required it.

19% (38/200) of our cohort underwent one or more surgeries secondary to complications of MMC. In total, 9 vesicostomies, 2 ureterostomies, 20 Mitrofanoff appendicovesicostomies, 26 bladder augmentations, and 7 Malone appendicostomies were performed. This does not consider the Achilles tendon release, a frequent event in children with MMC and which was not consulted in the survey.

Supplementation and maternal health

Of the mothers surveyed, only 32 (16%) took vitamin supplements preconceptionally, starting at least two months before the onset of pregnancy, but of these, only 24 (12%) included folic acid as part of the supplements. Moreover, 112 mothers (56%) reported bread consumption as part of their daily diet during pregnancy.

The four mothers who had previous children with NTDs reported not having received folic acid supplementation preconceptionally and two of them reported vitamin supplementation during gestation.

Regarding maternal health, 94 mothers presented some type of disease or condition at the time of pregnancy, the most frequent being migraine (11.5%), urinary tract infections (7.5%), hypertriglyceridemia (7%), anemia (5.5%), anxiety/panic disorder (5.5%), Crohn's disease (4.5%), diabetes mellitus (4.5%), depression (4%), and epilepsy (3%). Of the mothers with diabetes, 5/9 used hypoglycemic drugs during pregnancy, and 2 used preconception folic acid supplementation, while for mothers with epilepsy, only 3/6 took antiepileptic drugs during pregnancy, and one used folic acid supplementation in the periconceptional period.

Regarding maternal nutritional status before pregnancy, 13.5% (27/200) were diagnosed as obese, and 28.5% (57/200) were overweight.

Socioeconomic characteristics

When evaluating the level of education, 39.5% (79/200) of the family providers had tertiary-level education, and 96% (192/200) of the providers were employed at the time of the child's birth with MMC. In addition, 83.5% of the trios (167/200) had health insurance or coverage at the time of pregnancy.

Table 1. Sociodemographic characteristics of 200 families of Chilean people with myelomeningocele

	Clasificaction	(n)	(%)
Geographical distribution	MR	81	40.5
	North Macrozone	26	13
	Central Macrozone	35	17.5
	Central-South Macrozone	49	24.5
	South Macrozone	7	3.5
	Austral Macrozone	2	1
Sex	Male	89	44.5
	Female	111	55.5
Educaction level of the family supporter	None	5	2.5
	Primary	36	18
	Secondary	78	39
	Tertiary	79	39.5
	Doesn't know/doesn't answer	2	1
Employment situation of the supporter	Worker	192	96
	Unemployed	3	1.5
	Retired	0	0
	Other source of income	5	2.5
Health insurance	Yes	167	83.5
	No	30	15
	Doesn't know/doesn't answer	3	1.5

MR: Metropolitan Region

Table 2. Clinical characteristics of 200 Chilean people with myelomeningocele

	Clasificaction	(n)	(%)
Ntd level	High	14	7
	Low	166	83
	Doesn't know/doesn't answer	20	10
Gait*	Achieved with technical assistance	109	62.7
	Achieved without technical assistance	15	8.6
	Not achieved	50	28.7
Complications	neurogenic Bladder	148	74
	Hydrocephalus	148	74
	Chiari type 2 malformation	72	36
	Tethered cord	70	35
	Clubfoot	60	30
Interventions	Ventriculoperitoneal shunt	128	64
	Clean intermittent catheterization	126	63
	Vesicostomie	9	4.5
	Ureterostomie	2	1
	Mitrofanoff	20	10
	Bladder augmentation	26	13
	Malone	7	3.5

*Gait in people over 18 years old. NTD: neural tuve defect.

Discussion

This study is the first in Chile that allows us to characterize a sample of Chilean children with MMC, regarding clinical and sociodemographic aspects.

Most of the country's regions were represented, except for the Arica and Parinacota Region and the Aysén Region.

The methodology of this study does not allow us to determine differences by sex among those affected, nor if there was variation between the pre- and post-fortification periods due to the low number of pre-fortification cases included (26/200).

Prenatal diagnosis was achieved in 63.5% of cases, a lower detection rate than in European countries (90%)[19] and than the regional average for South America (93.9%)[20]. The rate of *in utero* surgical repair was also lower (15%) than other studies in North America, which report an eligibility for repair of up to 46%[21,22]. Improving the perinatal detection rate of this congenital anomaly would undoubtedly contribute to improving its management and prognosis of children with MMC.

A high cesarean rate was observed in our cohort (82.5%), exceeding the national cesarean delivery rate, which was reported at 43.6% for the first quarter of 2022 by the Undersecretariat of Healthcare Networks[23]. This significant increase may be related to the coordination between neurosurgical and obstetric teams to ensure early closure of the lesion, the presence of a recent prior hysterorrhaphy (as in the case of children undergoing *in utero* surgery), or the traditional consideration that cesarean delivery would result in better motor outcomes in infants by avoiding traction on the neural placode during vaginal delivery, a consideration that recent evidence has ruled out[15,24].

A higher preterm delivery rate of 19% (38/200) was observed when compared to the general preterm delivery rate in Chile for the year 2021 (9.5%)[25], an excess that may be explained in part by cesarean sections performed in pregnancies that underwent *in utero* repair (20/30), in addition to the increased tendency to have preterm delivery when the fetus presents congenital defects[26,27].

International descriptions highlight that the level of the MMC defect is commonly observed in the lumbosacral region[15], a characteristic also observed in our cohort (83%). Additionally, several North American reports have indicated that after the mandatory folate fortification, a significant decrease in high-level lesion cases and severity of the BS defect has been observed[28,29,30,31]. A low-level lesion is associated with a lower morbidity rate and a higher chance of achieving walking (30.5%)[31].

Ambulation largely depends on the level of the lesion, with most individuals with low-level lesions being able to walk[15], however, most children who achieve ambulation do so with the use of assistive devices. The ability to ambulate decreases in adulthood, a situation associated with surgical complications or weight gain[32]. In our cohort, 32.2% (40/124) of those who achieved ambulation had lesions at L5 or lower, 55.6% (69/124) had a lesion between L1 and L5, and only 4% (5/124) had a high cervical or thoracic spine lesion; on the other hand, 10 children with MMC who achieved ambulation, the level of their lesion could not be determined. The methodology of our study does not allow us to evaluate whether there was a decrease in ambulation capacity in adulthood. In addition, it is internationally reported that 50-60% of children with MMC require assistive devices for walking[33]. In our sample, this percentage was higher with up to 87.8% needing assistance, mainly ankle-foot orthoses.

Myelomeningocele produces several central nervous system anomalies, including tethered cord, neurogenic bladder, CM-II, and hydrocephalus, conditions that usually require surgical intervention, with VP shunt placement being frequent (up to 90% of children with MMC with postnatal repair)[34]. In our series, 70% (119/170) of the children with MMC with postnatal repair required VP shunt, while only 30% (9/30) of those with *in utero* surgery required VP shunt placement. These results are in line with those reported in the Management of Myelomeningocele Study (MOMS), which demonstrated a lower need for a VP shunt in children with *in utero* repair (40% at one year of life)[35].

Neurogenic bladder often presents with involuntary detrusor contractions (hyperreflexia), resulting in impaired urine storage or elimination, and has been reported in about 50% of children with open SB[17,36] and, in our group, it reaches 74% of cases. The use of CIC has been shown to reduce both the associated complications and renal morbidity related to neurogenic bladder, which is why its use continues to be recommended[17].

During growth, children with MMC may present neurological, urological, or orthopedic impairment, accompanied by foot or spinal deformities, pain, or spasticity. This is known as tethered cord, which is diagnosed clinically, though it should ideally be accompanied by neuroimaging to rule out other causes[18]. This complication was observed in 35% of our sample, while a North American report recorded an incidence of 23% in a group of 502 children with MMC[37]. Furthermore, among the 70 patients with tethered cord, 47% had associated clubfoot.

The low rate of supplementation intake in our sam-

ple stood out, where only 16% reported having taken at least one multivitamin supplement two months before pregnancy. This agrees with what was reported in a previous study of this group where 342 Chilean puerperal women were surveyed on prevention methods of congenital anomalies and it was determined that only 8.6% and 25.9% reported the use of vitamins and/or folic acid, respectively[38]. This suggests little progress in educating women of reproductive age about congenital anomaly prevention measures, or lack of awareness of the importance of folic acid supplementation. Notably, none of the mothers with previous children with NTDs received supplementation, even though this measure is recommended in these cases and the national perinatal care guidelines[39].

Among the diseases or health conditions at the time of pregnancy, 4.5% of our sample presented pregestational diabetes and 9.5% gestational diabetes. The use of folic acid supplementation has been reported to have protective effects in high-risk pregnancies (including diabetes and maternal obesity)[40,41], but only 22.2% of our cohort with pregestational diabetes used folic acid 2 months before gestation. Another chronic condition detected in the mothers of our cohort was epilepsy (3%), a disease whose association with MMC has been described mainly due to teratogenic effects of the drugs used to treat it, especially valproic acid[42], but only half of the pregnant women with a diagnosis of epilepsy in our cohort used anticonvulsant drugs.

A slight increase in the risk of SB has also been associated with maternal obesity (OR 2.24; 95%CI 1.86–2.69)[40,43], as well as a significant increase in the risk of infant mortality in children with SB born to mothers with underweight or obesity compared to those with normal weight (HR: 4.5 [1.08-16.72] and 2.6 [1.36-8.02], respectively)[44]. Given the methodology of our study, the BMI data at the time of gestation was not reliable, so the factor of maternal obesity or periconceptional underweight was not evaluated in this sample.

Another limitation of this study is the lack of data on independence in basic and instrumental activities of daily living, or on school or work insertion of children with MMC. This is because the survey applied was focused on identifying risk factors for the condition. It would be relevant for other studies to analyze these types of variables.

Although this is the first clinical and sociodemographic description of Chilean children with MMC, the sample is still small (considering the estimated total for Chile)[3]. Additionally, as this is a voluntary study, there is a selection and recall bias, considering the time lapse between the birth of the children with MMC and the time of the survey.

However, despite these limitations, the data presented can help to provide information on the clinical and social conditions of families with children with MMC, which is relevant both for future research and for the development of public policies to improve the quality of life of these individuals.

Conclusion

This study detected a low rate of prenatal diagnosis (63.5%), infrequent *in utero* repair of MMC (15%), and low use of folic acid supplementation (12%), while the other parameters evaluated are very similar to those reported in international literature.

This makes evident the need for further education of patients, families, and healthcare personnel, not only in MMC but also in congenital anomalies and how to prevent them. It is essential to know every aspect of the needs and burdens of children with MMC and their families in order to achieve the ultimate goal of medicine, to improve the quality of life of our patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Project funded by the Chilean Society of Pediatrics, protocol SChP210101

Acknowledgments

Special thanks to *Teletón Chile*, CORPSB, and the Prenatal Spina Bifida Repair Team – *Hospital Dr. Franco Ravera Zunino of Rancagua*, institutions that collaborated significantly for the realization of this study; as well as to Drs. Margaret Ross, Richard Finnell, and Philip Lupo co-investigators of the broad study of which this sample is part, in the aspect of molecular genetics, with whom we are part of the Neural Tube Defects International Data Consortium (NTD-IDC).

References

1. Fletcher JM, Brei TJ. Introduction: Spina bifida--a multidisciplinary perspective. Dev Disabil Res Rev. 2010;16(1):1-5. doi: 10.1002/ddrr.101. PMID: 20419765; PMCID: PMC3046545.
2. Lupo PJ, Agopian AJ, Castillo H, et al. Genetic epidemiology of neural tube defects. J Pediatr Rehabil Med. 2017;10(3-4):189-94. doi: 10.3233/PRM-170456. PMID: 29125517; PMCID: PMC8085973.
3. Copp AJ, Adzick NS, Chitty LS, et al. Spina bifida. Nat Rev Dis Primers. 2015;1:15007. doi: 10.1038/nrdp.2015.7. PMID: 27189655; PMCID: PMC4898641.
4. Kancherla V. Neural tube defects: a review of global prevalence, causes, and primary prevention. Childs Nerv Syst. 2023;39(7):1703-10. doi: 10.1007/s00381-023-05910-7. Epub 2023 Mar 8. PMID: 36882610.
5. Agopian AJ, Tinker SC, Lupo PJ, et al; National Birth Defects Prevention Study. Proportion of neural tube defects attributable to known risk factors. Birth Defects Res A Clin Mol Teratol. 2013;97(1):42-6. doi: 10.1002/bdra.23100. PMID: 23427344; PMCID: PMC4482342.
6. Bravo-Avila HM, Garcés-Granoble IG, Zambrano-Macias C. Espina bífida asociada a deficiencia de ácido fólico en embarazadas en América Latina. MQRInvestigar [Internet]. 19 de febrero de 2024 [citado 8 de octubre de 2024];8(1):2294-310. Disponible en: https://www.investigarmqr.com/ojs/index.php/mqr/article/view/1000
7. Lammer EJ, Sever LE, Oakley GP Jr. Teratogen update: valproic acid. Teratology. 1987;35(3):465-73. doi: 10.1002/tera.1420350319. PMID: 3114906.
8. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832-5. doi: 10.1056/NEJM199212243272602. PMID: 1307234.
9. Wagh K, Kancherla V, Dorsey A, et al. A global update on the status of prevention of folic acid-preventable spina bifida and anencephaly in year 2022. Birth Defects Res. 2024;116(5):e2343. doi: 10.1002/bdr2.2343. PMID: 38688860.
10. International Clearinghouse for Birth Defects Surveillance and Research Annual Report 2014. Rome, Italy: International Clearinghouse for Birth Defects Surveillance and Research, 2016. ISSN 0743-5703 The International Centre on Birth Defects - ICBDSR Centre.
11. European Commission, 2022. EU Science Hub, European Platform on Rare disease Restriction, EUROCAT, DATA, EUROCAT. Prevalence per 10,000 Births. Neural Tube Defects, 2015 to 2020. All Full Registries. [Internet]. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en.
12. Pardo R, Vilca M, Villarroel L, et al. Neural tube defects prevalence does not increase after modification of the folic acid fortification program in Chile. Birth Defects Res. 2022;114(7):259-66. doi: 10.1002/bdr2.1994. Epub 2022 Feb 26. PMID: 35218603.
13. Llanos A, Hertrampf E, Cortes F, et al. Cost-effectiveness of a folic acid fortification program in Chile. Health Policy. 2007;83(2-3):295-303. doi: 10.1016/j.healthpol.2007.01.011. Epub 2007 Mar 23. PMID: 17363103.
14. Cortés F, Mellado C, Pardo RA, et al. Wheat flour fortification with folic acid: changes in neural tube defects rates in Chile. Am J Med Genet A. 2012;158A(8):1885-90. doi: 10.1002/ajmg.a.35430. Epub 2012 Jun 18. PMID: 22711368
15. Bowman RM, Lee JY, Yang J, et al. Myelomeningocele: the evolution of care over the last 50 years. Childs Nerv Syst. 2023;39(10):2829-45. doi: 10.1007/s00381-023-06057-1. Epub 2023 Jul 7. PMID: 37417984
16. Marcati E, Meccariello G, Mastino L, et al. Myelomeningocele: Long-Term Neurosurgical Management. Adv Tech Stand Neurosurg. 2024;49:95-122. doi: 10.1007/978-3-031-42398-7_6. PMID: 38700682
17. Alarcón-Arias P, Pardo-Vargas RA, Passalacqua W, et al. Importancia de la evaluación del sistema urinario en pacientes adultos con espina bífida. Actual. Med. [Internet] 2018;103:(804):87-91 Doi: 10.15568/am.2018.804.re01
18. Díaz Sanhueza C, Pardo Vargas RA, Bustos P. Manifestaciones neurológicas asociadas a espina bífida en adultos [Neurological manifestations associated with spina bifida in adults]. Semergen. 2018;44(4):276-80. Spanish. doi: 10.1016/j.semerg.2017.09.003. Epub 2017 Nov 20. PMID: 29162473.
19. Meller C, Covini D, Aiello H, et al. Update on prenatal diagnosis and fetal surgery for myelomeningocele. Arch Argent Pediatr. 2021;119(3):e215-e228. English, Spanish. doi: 10.5546/aap.2021.eng.e215. PMID: 34033426.
20. Campaña H, Ermini M, Aiello HA, et al; Latin American Collaborative Study of Congenital Malformations Study Group. Prenatal sonographic detection of birth defects in 18 hospitals from South America. J Ultrasound Med. 2010;29(2):203-12. doi: 10.7863/jum.2010.29.2.203. PMID: 20103790.
21. AlRefai A, Drake J, Kulkarni AV, et al. Fetal myelomeningocele surgery: Only treating the tip of the iceberg. Prenat Diagn. 2019;39(1):10-5. doi: 10.1002/pd.5390. Epub 2018 Dec 10. PMID: 30536580.
22. Pan ET, Pallapati J, Krueger A, et al. Evaluation and Disposition of Fetal Myelomeningocele Repair Candidates: A Large Referral Center Experience. Fetal Diagn Ther. 2020;47(2):115-22. doi: 10.1159/000500451. Epub 2019 Jun 18. PMID: 31212296.
23. Informe Glosa 04 Primer Trimestre 2022. Subsecretaria de Redes Asistenciales Mayo 2022. Accesible en www.minsal.cl/wp-content/uploads/2021/05/ORD-2143-30-06-2022.pdf
24. Greene S, Lee PS, Deibert CP, et al. The impact of mode of delivery on infant neurologic outcomes in myelomeningocele. Am J Obstet Gynecol. 2016;215(4):495.e1-495.e11. doi: 10.1016/j.ajog.2016.05.028. Epub 2016 May 27. PMID: 27242203.
25. Departamento de Estadísticas e Información en Salud. MINSAL. (Acceso septiembre 22,2023). *Estadísticas de Nacimiento - SAS® Visual Analytics. Estadísticas de Nacimiento.* https:// informesdeis.minsal.cl/SASVisualAnalytics/
26. Ho P, Quigley MA, Tatwavedi D, et al. Neonatal and infant mortality

associated with spina bifida: A systematic review and meta-analysis. PLoS One. 2021;16(5):e0250098. doi: 10.1371/journal.pone.0250098. PMID: 33979363; PMCID: PMC8115829.
27. Pace ND, Siega-Riz AM, Olshan AF, et al; National Birth Defects Prevention Study. Survival of infants with spina bifida and the role of maternal prepregnancy body mass index. Birth Defects Res. 2019;111(16):1205-16. doi: 10.1002/bdr2.1552. Epub 2019 Jul 19. PMID: 31322328; PMCID: PMC7285624.
28. De Wals P, Tairou F, Van Allen MI, et al. Spina bifida before and after folic acid fortification in Canada. Birth Defects Res A Clin Mol Teratol. 2008;82(9):622-6. doi: 10.1002/bdra.20485. PMID: 18655127.
29. Parker SE, Yazdy MM, Mitchell AA, et al. A description of spina bifida cases and co-occurring malformations, 1976-2011. Am J Med Genet A. 2014;164A(2):432-40. doi: 10.1002/ajmg.a.36324. Epub 2013 Dec 19. PMID: 24357196; PMCID: PMC4353584.
30. Bergman JE, Otten E, Verheij JB, et al. Folic acid supplementation influences the distribution of neural tube defect subtypes: A registry-based study. Reprod Toxicol. 2016;59:96-100. doi: 10.1016/j.reprotox.2015.11.007. Epub 2015 Nov 25. PMID: 26627544.
31. Mai CT, Evans J, Alverson CJ, et al. Changes in Spina Bifida Lesion Level after Folic Acid Fortification in the US. J Pediatr. 2022;249:59-66.e1. doi: 10.1016/j.jpeds.2022.06.023. Epub 2022 Jun 27. PMID: 35772508; PMCID: PMC10250025.
32. Cortez C, Schulz R, Pardo R. Espina bífida en adultos: Una revisión de las alteraciones musculoesqueléticas. Archivos de Medicina 2017;13(2):12. doi: 10.3823/1352
33. Kellogg R, Lee P, Deibert CP, et al. Twenty years' experience with myelomeningocele management at a single institution: lessons learned. J Neurosurg Pediatr. 2018;22(4):439-43. doi: 10.3171/2018.5.PEDS17584. Epub 2018 Jul 13. PMID: 30004312.
34. Tennant PW, Pearce MS, Bythell M, et al. 20-year survival of children born with congenital anomalies: a population-based study. Lancet. 2010;375(9715):649-56. doi: 10.1016/S0140-6736(09)61922-X. Epub 2010 Jan 19. PMID: 20092884.
35. Adzick NS, Thom EA, Spong CY, et al; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011 Mar 17;364(11):993-1004. doi: 10.1056/NEJMoa1014379. Epub 2011 Feb 9. PMID: 21306277; PMCID: PMC3770179.
36. Freeman KA, Castillo H, Castillo J, et al. Variation in bowel and bladder continence across US spina bifida programs: A descriptive study. J Pediatr Rehabil Med. 2017;10(3-4):231-41. doi: 10.3233/PRM-170450. PMID: 29125511; PMCID: PMC7909989.
37. Bowman RM, Mohan A, Ito J, et al. Tethered cord release: a long-term study in 114 patients. J Neurosurg Pediatr. 2009;3(3):181-7. doi: 10.3171/2008.12.PEDS0874. PMID: 19338463.
38. Pardo VRA, Lay-Son RG, Aranda ChW, et al. Conocimiento sobre el ácido fólico en la prevención de defectos de cierre del tubo neural: una encuesta a mujeres que viven en Santiago de Chile [Awareness and knowledge of the use of folic acid in the prevention of neural tube defects: a survey of women living in Santiago, Chile]. Rev Med Chil. 2007;135(12):1551-7. Spanish. Epub 2008 Feb 13. PMID: 18357356.
39. Guia Perinatal 2015, Subsecretaría de Salud Pública, División Prevención y Control de Enfermedades Departamento de Ciclo Vital, Programa Nacional Salud de la Mujer. Ministerio de Chile, accesible a través de: https://www.minsal.cl/sites/default/files/files/GUIA%20PERINATAL_2015_%20PARA%20PUBLICAR.pdf
40. Parker SE, Yazdy MM, Tinker SC, et al. The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida. Am J Obstet Gynecol. 2013;209(3):239.e1-8. doi: 10.1016/j.ajog.2013.05.047. Epub 2013 May 24. PMID: 23711668; PMCID: PMC3989866.
41. Petersen JM, Parker SE, Crider KS, et al. One-Carbon Cofactor Intake and Risk of Neural Tube Defects Among Women Who Meet Folic Acid Recommendations: A Multicenter Case-Control Study. Am J Epidemiol. 2019;188(6):1136-43. doi: 10.1093/aje/kwz040. PMID: 30976786; PMCID: PMC6545279.
42. Lisi A, Botto LD, Robert-Gnansia E, et al. Surveillance of adverse fetal effects of medications (SAFE-Med): findings from the international Clearinghouse of birth defects surveillance and research. Reprod Toxicol. 2010;29(4):433-42. doi: 10.1016/j.reprotox.2010.03.005. Epub 2010 Mar 27. PMID: 20347959.
43. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009;301(6):636-50. doi: 10.1001/jama.2009.113. PMID: 19211471.
44. Pace ND, Siega-Riz AM, Olshan AF, et al; National Birth Defects Prevention Study. Survival of infants with spina bifida and the role of maternal prepregnancy body mass index. Birth Defects Res. 2019;111(16):1205-16. doi: 10.1002/bdr2.1552. Epub 2019 Jul 19. PMID: 31322328; PMCID: PMC7285624.