MINISTRY OF HEALTH OF BRAZIL

HEALTH BRAZIL 2020/2021

PRIORITY CONGENITAL ANOMALIES FOR SURVEILLANCE AT BIRTH

Brasília DF 2022

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Secretariat of Health Surveillance
Department of Health Analysis and
Noncommunicable Diseases Surveillance

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Summary

PRESENTATION

This is the first edition of the book *Health Brazil: priority congenital anomalies for surveillance at birth*, prepared by the General Coordination of Epidemiological Information and Analysis (Cgiae), the Department of Health Analysis and Noncommunicable Diseases Surveillance (DASNT), the Secretariat of Health Surveillance (SVS) of the Brazilian Ministry of Health, in partnership with the Universidade Federal do Rio Grande do Sul (UFRGS), and Hospital de Clínicas de Porto Alegre (HCPA), and with the help of a group of specialists in the field.

Congenital anomalies represent a group of structural or functional changes that occur during intrauterine life and are an important cause of chronic diseases, disabilities, as well as fetal mortality, in newborns and in children. It is estimated that between 2% and 3% of all newborns have some kind of congenital anomaly in the world.

In 2010, the 63rd Assembly of the World Health Organization urged all countries to prevent congenital anomalies, stimulating the promotion of screening programs, as well as support and care for individuals with congenital anomalies and their families. In addition, the topic of congenital anomalies has gained prominence worldwide since 2015, due to the occurrence of an epidemic of microcephaly (a type of anomaly that is characterized by the reduction of the head circumference) and other clinical findings associated with intrauterine infection by the Zika virus, initially identified in Brazil and later observed in other Latin American countries. At the time, the Brazilian Ministry of Health developed a series of actions within the scope of surveillance and health care of children with this new pathological entity, which became known as Congenital Zika Syndrome (CZS).

In 2017, with the official closure of the public health emergency period related to CZS in Brazil, it was identified that there is a need to expand the surveillance strategy for CZS to include other anomalies, regardless of the cause, thus enabling the identification of these diseases in a timely manner to carry out interventions aimed at improving the quality of life of affected individuals. Thus, since 2019, SVS has a technical area dedicated to the structuring and implementation of active surveillance of congenital anomalies in the Country.

Moreover, collaboration is a keyword among national congenital anomalies surveillance programs around the world, which commonly focus and are organized in surveillance networks to strengthen local surveillance, standardize definitions and methods of capturing cases, compare epidemiological findings and prevention measures, among othersi. Thus, this publication may be useful for other countries that, like Brazil, aim to structure a national surveillance of congenital anomalies.

The main objective of this book is to provide theoretical and practical information on the recognition and surveillance of congenital anomalies at birth, in order to strengthen their registration in Official Information Systems (in the case of Brazil, in the Live Birth Information System, or Sinasc, in Portuguese) and enable the qualification of health policies.

Since 1990, Sinasc gathers information on all births in Brazil and has international prominence, as one of the largest and most complete birth information systems around the world[i]. However, there is clear spatio-temporal heterogeneity in the reporting of anomalies at the national level and, in most cases, such variability can be attributed to under-registration or misregistration of certain types of anomalies.

In order to improve the quality of the registration of anomalies in Sinasc, it was identified that there is a need to establish a list of priority anomalies for birth surveillance. Thus, the Brazilian Ministry of Health, in consensus with experts on the subject, proposed a priority list of eight groups of congenital anomalies for which birth surveillance and notification in Sinasc need to be strengthened, based on two main criteria: being diagnosable at birth, or shortly after it, and having preventive and corrective intervention at different levels. The complete list is presented in Chart 1 and the process of its construction is documented in an open access scientific manuscript published in the *Epidemiology and Health Services* journal[ii]. It is important to ratify that, in Brazil, as established in Law No. 13.685/2018, all congenital anomalies identified by the physician during gestation or at the time of delivery should be described in the Live Birth Declaration (DNV, in Portuguese) and recorded in Sinasc. However, the focus on a specific number of anomalies is strategic for surveillance, since it allows the adoption of more effective strategies for training health professionals who perform their recognition and make the notification in the system.

[i] CARDOSO-DOS-SANTOS, A. C. *et al*. Redes de colaboración internacional para la vigilancia de anomalías congénitas: una revisión narrativa. **Epidemiol. Serv. Saude**, v. 29, n. 4, p. e2020093, 2020. DOI: https://doi.org/10.5123/s1679-49742020000400003. Available at: https://www.scielo.br/j/ress/a/ssZpHBFtPT5mjBYrVFDQXcz/?format=html. Access on: 5 apr. 2021.

[ii] CARDOSO-DOS-SANTOS, A. C. *et al*. Lista de anomalías congénitas prioritarias para la vigilancia bajo el Sistema de Información sobre Nacidos Vivos en Brasil. **Epidemiol. Serv. Saude**, v. 30, n. 1, p. e2020835, 2021. DOI: https://doi.org/10.1590/S1679-49742021000100030. Available at: https://www.scielo.br/j/ress/a/7XZrfFncXf964hFGMk6Ftzv/?lang=pt. Access on: 5 apr. 2021.

Chart 1 – List of priority congenital anomalies for birth surveillance and registration strengthening in the Live Birth Information System (Sinasc), classified according to ICD-10 – Brazil, 2021

GROUP OF ANOMALIES	ICD-10 COD	DESCRIPTION
Neural Tube Defects	Q00.0	Anencephaly
	Q00.1	Craniorachischisis
	Q00.2	Iniencephaly
	Q01	Encephalocele
	Q05	Spina bifida
Microcephaly	Q02	Microcephaly
Congenital heart disease	Q20	Congenital malformations of cardiac chambers and communications
	Q21	Congenital malformations of the heart septa
	Q22	Congenital malformations of the pulmonary and tricuspid valves
	Q23	Congenital malformations of the aortic and mitral valves
	Q24	Other congenital malformations of the heart
	Q25	Congenital malformations of the great arteries
	Q26	Congenital malformations of great veins
	Q27	Other congenital malformations of the peripheral vascular system
	Q28	Other congenital malformations of the circulatory system
Oral clefts	Q35	Cleft palate
	Q36	Cleft lip
	Q37	Cleft lip with cleft palate
Anomalies of Genital Organs	Q54	Hypospadias
	Q56	Indeterminate sex and pseudo-hermaphroditism
Limb Defects	Q66	Congenital deformities of the foot
	Q69	Polydactyly
	Q71	Defects, by reduction, of the upper limb
	Q72	Defects, by reduction, of the lower limb
	Q73	Unspecified limb reduction defects
	Q74.3	Multiple congenital arthrogryposis
Abdominal Wall Defects	Q79.2	Exonphalia
	Q79.3	Gastroschisis
Down Syndrome	Q90	Down Syndrome

Source: CARDOSO-DOS-SANTOS, A. C. et al. Lista de anomalías congénitas prioritarias para la vigilancia bajo el Sistema de Información sobre Nacidos Vivos en Brasil. **Epidemiol. Serv. Saude**, v. 30, n. 1, p. e2020835, 2021. DOI: https://doi.org/10.1590/S1679-49742021000100030. Available at: https://www.scielo.br/j/ress/a/7XZrfFncXf964hFGMk6Ftzv/?lang=pt. Access on: 5 apr. 2021.

This book is divided into two parts: (i) review the main clinical characteristics of congenital anomalies listed as priorities for birth surveillance; and (ii) reports on the experiences of Brazilian teams, acting at the national and local level to deal with the CZS epidemic, in addition to exploring tools that can help in the process of identification, coding and surveillance of congenital anomalies.

Proper notification is the first step towards the organization of national surveillance of congenital anomalies. By strengthening our existing system, we will be able to evaluate the real impact of anomalies on populations, in addition to producing useful information to promote prevention and care measures adjusted to the reality of each part of the world. For this, it is essential that professionals and institutions recognize the importance of congenital anomalies in the context of public health and register all those diagnosed at birth in official information systems.

Secretariat of Health Surveillance
Ministry of Health of Brazil

PART I

REVIEWING PRIORITY CONGENITAL ANOMALIES

1 CONGENITAL ANOMALIES AND THE IMPORTANCE OF NOTIFICATION

SUMMARY

OBJECTIVE

To present an introduction on congenital anomalies (CA), addressing conceptualization, epidemiology, risk factors, classification, embryonic development, prevention strategies, as well as aspects related to the notification of these health conditions.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

CA are changes that occur during embryonic/fetal development and affect the structure or function of the body, having different causes and, in many cases, it can be multifactorial. They can be classified into malformations, disruptions, deformities and dysplasia. CA have a great impact on the individual, family and health system. They are associated with high rates of morbimortality. However, approximately 50% of CA are preventable. The treatment indicated may be surgical, or be restricted to supportive therapies. Genetic counseling is recommended in many situations. The early diagnosis and its registration in the Live Birth Declaration are fundamental to produce epidemiological data for monitoring, therefore, the planning of attention and prevention strategies.

CONCLUSION

CA are health problems of great importance for public health, considering the large number of individuals affected by these conditions, and the possibility of creating primary and tertiary prevention policies. In this context, the act of notifying a CA on the birth declaration is able to provide a chain of events that will directly impact individuals, their family and the health system.

KEYWORDS

Congenital abnormalities. Information systems. Surveillance in public health. Epidemiological surveillance.

INTRODUCTION

Congenital anomalies (CA) are changes that occur during embryonic/fetal development and that affect the structure or function of the body. Many cause disabilities and compromise the full development of the individual (Table 1). CA can be diagnosed during prenatal care or at birth, such as anencephaly, which is a malformation; after birth or later in life, such as some kind of congenital heart defects.[1] It is important to note that not all CA have genetic causes.

It is estimated that CA are present in about 3% to 6% of births worldwide.[2] In Latin America, this prevalence is 5%, however, these data may be underrepresented due to poor recording. Approximately 94% of all CA cases occur in low and middle-income countries and each year CA are responsible for more than 300,000 neonatal deaths worldwide. Among severe CA, neural tube defects (NTD), congenital heart disease and Down syndrome (DS) stand out.[2]

CA can have a great impact on the individual, family and socioeconomic conditions, either by its clinical prognosis, risk of recurrence in the family, as well as elevated cost for the health system due to chronicity and the need for multidisciplinary care, often of high complexity.[3,4] Timely identification of CA facilitates adequate diagnosis and treatment, and can guide primary, secondary and tertiary prevention strategies. Thus, this chapter aims to address morphological or anatomical CA, etiology, risk factors, pathophysiogenesis, morbidity and prevention.

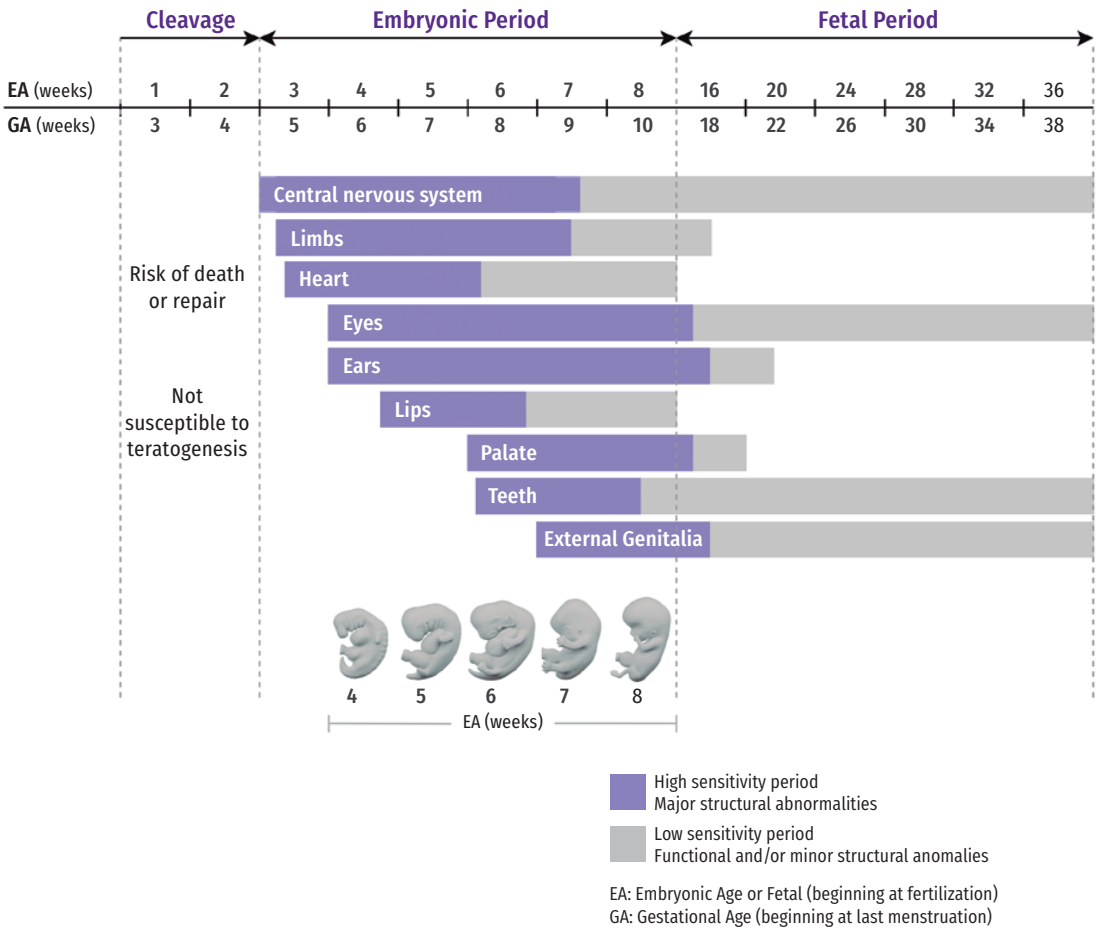
When do congenital anomalies occur? A little about embryofetal development

During pregnancy, there are critical periods when concepts are more susceptible to agents or factors that lead to abnormal development. Prenatal development can be divided into embryonic and fetal period.

The embryonic period begins from fertilization (union of the oocyte with the sperm) and formation of the zygote. At this time, there is a number of mitotic divisions that lead to the development of a set of cells called morula, with totipotent cells, with total capacity for regeneration. Morula undergoes a cavitation process giving rise to the blastocyst that at the end of the first week of development begins the implantation process in the uterus. Between the second and third week of embryonic development, the implantation is consolidated and the gastrulation process also occurs, the result of which is the establishment of the three embryonic leaflets, which will give rise to all tissues and organs of the body. In general, changes and/or aggressions that occur in this period are unlikely to result in a defective development. Changes in this phase lead to the death of the embryo or are compensated by the regulatory properties of the initial embryo.[5]

Between the 3rd and 8th weeks of development, most organs and regions of the body are established. This period, known as the period of organogenesis, is of maximum susceptibility to the development of abnormal structures. If some physical, chemical, intrinsic factor (genetic or not) intervenes in this period of development, congenital anomalies can happen. In Chart 1, it is possible to observe the period of greatest and least susceptibility to congenital anomalies, showing the sensitivity by organ.

Chart 1 – Schematic illustration showing the periods of intrauterine development and the susceptibility of different organs and structures to teratogens



Source: authors, adapted from MOORE, K. L.; PERSAUD, T. V. Defeitos Congênitos Humanos. In: MOORE, K. L.; PERSAUD, T. V. **Embryology Clínica**. 10. ed. Rio de Janeiro: Guanabara Koogan, 2016. p. 161-193; CARLSON, B. M. **Embryology Humana e Biologia do Desenvolvimento**. 5. ed. Rio de Janeiro: Elsevier, 2014.

Note: In the first two weeks ("all or nothing") the teratogen damages all the cells of the embryo leading to death or it regenerates completely and does not show changes. Purple bars indicate periods of high sensitivity to teratogens, which can cause major defects in the indicated organs and structures. Gray bars have a period of low sensitivity to teratogens, where structural, functional or minor anomalies can be established. EA/F: embryonic or fetal age in weeks (onset at conception); GA: gestational age in weeks (onset at last menstruation).

After the period of organogenesis, the embryonic period ends and the fetal period begins, which goes until birth. In the fetal period some structures that began development in the embryonic period are consolidated, such as the closure of the cleft palate. Some systems follow their development in the fetal period, such as the respiratory and nervous systems. There is a lower probability of occurrence of structural congenital anomalies in this period. Anomalies that arise in the fetal period tend to be functional (for example, intellectual disability) or involve disorders in the growth of fetal structures.[5–8]

What are the main causes of congenital anomalies?

CA can be caused by genetic, environmental or multifactorial factors. In this case, they occur in isolation by a combination of genetic predisposition and environmental factors (multifactorial inheritance), and can understand the interaction between gene-gene and gene-environment, known as **multifactorial**.

Genetic causes are classified as monogenic and chromosomal. Monogenic are called those determined by changes in a single gene. These can be inherited or happen by chance (new or repeated mutation). When inherited, they can occur in different ways. In the autosomal dominant mode, the child can inherit from one of the parents the mutation that causes CA, forming a set of characteristics that can be called syndrome or sequence, as will be seen below. The mutation can also be inherited from both parents, even if they do not have any CA. In this case, the inheritance is known as autosomal recessive and the parents are said to be carriers and, the offspring, affected.[1] A third mode of inheritance is sex-linked or X-linked, in which the carrier mother carries on one of her X chromosomes a mutation and transmits it to male children.[9]

Problems in the number or structure of chromosomes also cause CA. These problems occur when there is a failure in the separation of chromosomes during cell division, a process that is called nondisjunction and which can occur more often when the pregnant woman is 35 years old or older.

Congenital anomalies can also be caused by environmental factors, called teratogens, which are agents external to the developing embryo, and account for 7% to 10% of the causes of CA.[10,11] They can be physical, chemical, biological, mechanical or nutritional agents, which include maternal conditions, infections, heavy metal ingestion/intoxication, medication and drug use, radiation exposure, among others.[10] Human teratogens are particularly difficult to identify, either by epidemiological surveillance systems or by clinical observations. Due to this, only a small share of external agents is recognized as teratogens or has their associated anomalies well described.[12] Chart 1 contains a list of some human teratogens already described and their associated anomalies. For most of them, identification took place through case reports by doctors.

Chart 1 – Main known teratogens in humans and their most frequent congenital anomalies

	TERATOGENS	RELATED CA IN HUMANS
Physical and Chemical	Ionizing radiation (doses above 5Sv)	Microcephaly, intellectual disability, skeletal abnormalities and intrauterine growth restriction
	Mercury	Anomalies of the central nervous system
	Lead	Prematurity, cardiac abnormalities and limb abnormalities
	Polychlorinated Biphenyl	Intrauterine growth restriction
Drugs and Medicines	Alcohol	Fetal alcohol syndrome (microcephaly, facial dysmorphia, cardiac and central nervous system abnormalities, pre and postnatal growth restriction), behavioral disorders, learning difficulty, memory and attention
	Tobacco	Oral clefts, prematurity, intrauterine growth restriction and neurodevelopment abnormalities (Attention deficit/ hyperactivity disorder)
	Cocaine	Low birth weight, intrauterine growth restriction, prematurity, central nervous system abnormalities, microcephaly and neurobehavioral disorders
	Thalidomide	Phocomelia and other limb reduction defects, microphthalmia, microtia, cardiac abnormalities and renal Agenesis
	Warfarin	Eye abnormalities, nasal hypoplasia, central nervous system abnormalities
	Retinoids	Microtia, cardiac and central nervous system abnormalities
	Carbamazepine	Neural tube closure defects
	Valproic Acid	Neural tube closure defects, valproic acid embryopathy (craniofacial and cardiovascular abnormalities, intrauterine growth restriction), neurobehavioral disorders
	Lithium	Cardiovascular abnormalities
	ACE inhibitors	Renal dysplasia, renal failure, oligohydramnios, intrauterine growth restriction and deformities of oligohydramnios sequence.
	Methotrexate	Neural tube closure defects, hydrocephalus and skeletal anomalies
	Misoprostol	Neurological abnormalities (congenital facial paralysis, other cranial paralysis), limb reduction defects (amputation type), clubfoot.
	Diethylstilbestrol	Abnormalities of the reproductive system, increased incidence of vaginal cancer in female offspring
	Tetracycline	Anomalies in tooth enamel
	Androgens	Virilization of the external genitalia in fetuses 46, XX

To be continue

continuation

	TERATOGENS	RELATED CA IN HUMANS
Biological agents	Toxoplasmosis	Microcephaly, chorioretinitis, intellectual disability, ventriculomegaly, hydrocephalus, hepatosplenomegaly and Epilepsy
	Rubella	Heart abnormalities, deafness, cataracts, microphthalmia and other eye abnormalities, intellectual disability, microcephaly, cerebral palsy and intrauterine growth restriction
	Cytomegalovirus	Sensorineural deafness, convulsions, jaundice, hepatosplenomegaly, intrauterine growth restriction and Microcephaly
	Syphilis	Chorioretinitis, intellectual disability, osteochondritis, jaundice, hepatosplenomegaly, intrauterine growth restriction, deafness, hydrocephalus and facial abnormalities
	HIV	Intrauterine growth restriction, postnatal microcephaly
	ZIKV	Microcephaly and disruptive brain abnormalities, hypertonia, arthrogryposis, facial dysmorphia
Maternal conditions	Severe obesity	Neural tube closure defects
	Diabetes mellitus	Cardiovascular defects, neural tube closure defects, central nervous system defects, macrosomia, skeletal defects and tail dysplasia
	Folic acid deficiency	Neural tube closure defects
	Iodine deficiency	Congenital hypothyroidism, neurological damage (cognitive and intellectual disability)
	Hyperthermia	Neural tube closure defects

Source: authors.

For more information see the National System of Information on Teratogens (Siat): www.gravidezsegura.org

It was only from the 1940s that environmental factors were recognized as causing congenital anomalies and other gestation outcomes. The first evidence of this was a report of cases of congenital cataracts in infants with intrauterine exposure to rubella.[13] The teratogenic action of an agent will depend on different factors, such as the dose and period of exposure to the agent during pregnancy.[11,14] The window of teratogenic action of an agent is an important characteristic and refers to the period of gestation in which the organs and tissues recognized to be affected by this agent have greater sensitivity to it, that is, a period with greater risk that this teratogen will cause the observed anomalies. It is important to note that this window of action is responsible for the observed CA for each agent, in addition to that, exposures in different periods within the teratogenic window of action for the same teratogen may confer different anomalies.[15] Thus, the effects of a teratogen are usually observed in a specific pattern of CA or a specific anomaly during a sensitive period of gestation with a dose-dependent effect.

Most teratogen-related abnormalities are due to maternal conditions (Chart 1). Chronic maternal diseases and changes in metabolism such as diabetes and possibly obesity are related to the occurrence of CA, diabetes being an important risk to cardiac abnormalities[16] and to neural tube closure defects (NTD).[17]

Congenital infections are also a cause of CA within environmental factors, being considered a class of biological type teratogens. Its clinical and epidemiological relevance is such that the main diseases were grouped into the so-called "STORCH", referring to syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex 1 and 2.[1] The most recent example of congenital infection as a risk factor for abnormalities, the Zika virus, gained notoriety from 2015 when it was associated with the increased incidence of microcephaly in newborn children of pregnant women infected during gestation.[18]

Licit and illicit drugs, with medications, chemical agents and physical agents, represent around 1% of the causes of CA.[11] Of the licit drugs, it is noteworthy that there is no safe dose for the consumption of alcoholic beverages that guarantees the normal development of the embryo, and there may be the development of fetal alcohol syndrome (FAS). The use of medicines during pregnancy should be supervised by a health professional, who should assess the risks and benefits of their use, as well as the dose and the gestational age in progress, due to the large number of drugs associated with the development of congenital anomalies, the most recognized being anticonvulsants, thalidomide, retinoic acid and warfarin (Chart 1).[19]

The medication with teratogenic action best documented is thalidomide, due to the so-called “thalidomide tragedy” that occurred in the early 1960s, in which more than 10 thousand children were affected by the teratogenic effects of the medication. The set of congenital anomalies caused by thalidomide is known as thalidomide embryopathy and includes limb malformations, mainly phocomelia, malformations of the heart, eyes and ears.[20] In Brazil, this medication is still causing of congenital anomalies in newborns.[21-23]

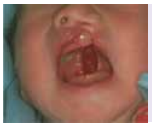
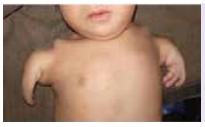
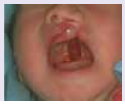
Maternal exposure to chemicals such as lead and mercury may increase the risk of CA, especially malformations. In addition, the unfavorable socioeconomic situation can be an indirect determinant for CA, and 94% of important congenital anomalies occur in middle and low-income countries. This is possibly due to the lack of access of pregnant women to adequate nutrition, greater exposure to infections and less access to health care.[2]

How do we classify congenital anomalies?

Regarding morbidity, CA are classified as minor and major (Figure 1). Minor CA are derived from the fetal period and generally do not cause significant problems, being the most frequent in the population. However, it should be checked if their occurrence is isolated, since the presence of two or more smaller CA may indicate larger internal anomalies. Of the children born with three or more minor abnormalities, 90% present a major abnormality, requiring thorough investigation. Examples of minor anomalies are preauricular appendages, digitiform polydactyly and hypospadias (Figure 1).

Figure 1 – Classification of congenital anomalies

HOW DO WE CLASSIFY CONGENITAL ANOMALIES?

CLASSIFICATION AS:	SUBTYPES AND THEIR DEFINITION		EXAMPLE
MORBIDITY	Minor malformations	They do not cause significant problems, being the most frequent in the population.	 Polydactyly
	Major malformations	They originate in the embryonic period and constitute structural abnormalities with social and/or medical consequences, being less frequent in the population.	 Oral clefts
PATHOGEN	Malformation	They are the result of problems in the process of organ formation or structures (abnormal or incomplete).	 Syndactyly
	Disruption	Result of extrinsic disruption or interference that occurs in a process of formation of an organ or part of the body.	 Phocomelia by Thalidomide
	Dysplasia	Resulting from abnormality in the histogenesis of one or more tissues.	 Skeletal dysplasia
	Deformity	Initial development occurs normally, however, given the action of mechanical forces the structure deforms.	 Clubfoot due to myopathy
CLINICAL PRESENTATION	Isolated	Presence of only one congenital anomaly.	 Iris Coloboma
	Sequence	A succession of changes or errors triggered by the same malformation, disruption or deformity.	 Sequence by Pierre Robin
	Syndrome	It is a set of congenital anomalies that have a pathological relationship, but do not constitute a sequence.	 Down syndrome
	Association	A set of congenital abnormalities that occur with a higher frequency than expected for random combinations.	VACTERL Association **V**: Vertebral Malformation **A:** Anal atresia **C:** Cardiac changes **TE:** Tracheoesophageal Fistula **R:** Renal abnormalities **L:** Anomalies of limbs (Limbs)
	Multiple congenital anomaly	Presence of two or more major congenital anomalies that are not related, a reflection of a random association that does not constitute a syndrome or a sequence already described.	 Omphalocele  Oral clefts

Source: WHO; CDC; ICBDSR. **Birth defects surveillance**: atlas of selected congenital anomalies. Geneva: WHO, 2014.

The largest CA originate in the embryonic period and constitute structural abnormalities with social and/or medical consequences, being infrequent in the population. In general, they require medical or surgical interventions. Such abnormalities are the main responsible for mortality, morbidity and disability rates related to birth defects.[9] Examples are: oral clefts, lip-palatine clefts, anencephaly, Down syndrome and congenital heart disease.[24]

CA can also be classified according to their pathogenesis, such as malformation, disruption, dysplasia or deformity. They are called **malformations** structural CA that occur in an organ, part of an organ or in more extensive regions of the body and that are the result of problems in the process of formation, in the organogenesis of the structures in question, which may not form, or form abnormally or incompletely. **Disruption** is the term designated to refer to a structural anomaly that, like malformations, can occur in an organ, part of an organ or in a larger area of the body, however, unlike the malformation, the disruption does not result from an incorrect formation but from the interruption or extrinsic interference that occurs in a process of formation that would occur in a normal way. An example of this are structural changes arising from congenital infections, (rubella, syphilis, cytomegalovirus), ionizing radiation, medications (thalidomide, tetracyclines, hydantoin) and/or drugs (alcohol, cocaine). Structural changes arising from the action of amniotic flanges – fibrous bands that originate in the amniotic sac and that have the ability to curl in the body of the fetus, are also considered disruptions.[25]

The CA resulting from abnormalities in histogenesis, of one or more tissues, as well as the morphological consequences of these changes is given the name of **dysplasia**. Dysplasia, in general, affect tissues such as the skin, brain, cartilage or bones, and can affect tissues in a localized or generalized way, for example: achondroplasia, hemangioma, ectodermal dysplasia. A **deformity**, on the other hand, is a CA in the shape or position of a certain part of the body arising from the action of mechanical forces on this structure after its initial development, that is, the initial development occurs in a normal way, however, given the action of mechanical forces the structure deforms, for example: *Facies* from Potter, congenital dislocation of the hip, asymmetry of the hip, clubfoot by myopathy.[26]

Furthermore, CA can be classified according to their clinical presentation, being divided into isolated anomaly, sequence, syndrome or multiple congenital anomaly, association or syndrome. An **isolated anomaly** is the one that presents itself in an individual way and the newborn does not present another related anomaly. To the set of related abnormalities that supposedly or knowingly originate from a single defect or primary mechanical factor, is given the name of **sequence**. The sequence represents a succession of changes or errors triggered by the same malformation, disruption or deformity, such as: oligohydramnios sequence, Pierre Robin sequence. Sequences are considered isolated anomalies, except when they constitute part of a syndrome.[26] The **syndrome** is a set of CA that presents a pathological relationship but does not constitute a sequence. It can be a result of genetic, environmental or interaction factors. Examples of syndromes include trisomy 21 (Down syndrome), the result of a chromosomal abnormality, and congenital rubella syndrome, which is the result of an infection.[25]

The combination of congenital abnormalities that occurs more frequently than expected for random combinations is called association. An example is the **association** known by the acronym VACTERL and characterized by the presence of vertebral anomalies, anal atresia, cardiac anomalies,

tracheoesophageal fistula, renal anomalies and limb anomalies. When there is the presence of two or more larger CA that are not related, a reflection of a random association that does not constitute a syndrome or a sequence already described, there is a **multiple congenital anomaly**.[25,26]

Is there treatment for congenital anomalies?

Most CA is amenable to surgical treatment, which can correct or reduce fatal or disabling repercussions of birth defects, slowing their morbidity and mortality. Here, we highlight the great progress that cardiac surgery has made in the treatment of congenital heart diseases that are the most frequent group of CA. Thus, the precocity of identification and referral is fundamental and in some, such as hydrocephalus, prenatal diagnosis is decisive for therapeutic planning. For conditions in which surgical intervention is not possible, physical and motor, speech-language therapy and occupational therapy are adjuvants in the training of individuals with neuropsychomotor development involvement to better social integration.

Considering CA components of the scope of genetic diseases, genetic counseling and psychological support constitute a primary aspect in the support of the child and his family by informing about the condition, its repercussions, recurrence rates and therapeutic possibilities. These measures enable informed decision-making.[1]

How can we prevent birth defects?

Strategies for the prevention of congenital anomalies are of extreme importance during the planning and monitoring of pregnancy. Before conception, health teams can assist in reproductive planning, assessing the woman's health situation and helping to clarify doubts regarding pregnancy. In the same way, prenatal care becomes important for the prevention of CA through examinations, nutritional supplementation, vaccination, infection prevention, among others. Follow-up examinations such as the evaluation of fetal anatomy by detailed ultrasound and fetal echocardiography may be requested for complementary clinical evaluation.[27]

Interventions recommended by the WHO as a strategy to prevent CA include combating inadequate nutrition by ensuring that young and pregnant women have access to a varied and balanced diet aimed at adequate consumption of vitamins and minerals. Supplementation of vitamins and compounds can and should be carried out during prenatal care. Folic acid supplementation in the periconceptional period is important for the Prevention of neural tube abnormalities.[28] Iron supplementation is indicated during prenatal and up to the third postpartum month for the prevention of low birth weight, anemia and iron deficiency in the pregnant woman.[29,30] Other supplements that should be evaluated by the health professional and that are recommended in specific contexts are: calcium, vitamin A and iodine. Supplementation of vitamins C, D and E is not recommended to improve maternal and perinatal outcomes.[30]

Vaccination of the pregnant woman should be recommended by the health professional taking into account the individual risks of each pregnancy. Influenza and dTpa vaccines (diphtheria, tetanus and whooping cough), which should be carried out between the 27th and 36th week, are indicated for all pregnant women, safe for the mother and for the baby.[31] Proper planning of vaccination can prevent the occurrence of congenital infections and should be evaluated according to the

risks and benefits, taking into account the geographical regions in which the pregnant women are located. In the same way, the detection, prevention and treatment of maternal infections such as STORCH are important, and examinations for infections are indicated.

In addition to follow-up examinations, supplementation and vaccination, other CA prevention strategies include the control of maternal diseases such as diabetes disease and obesity.[2] It is also advisable to inform the pregnant woman about the possible outcomes after the use of drugs, licit and illicit, or exposure to other environmental substances, such as heavy metals and pesticides, in order to avoid maternal exposure to possible teratogens.[2] The role of the health professional is also relevant in informing the mother about the use of medications without a doctor's prescription or without assessing the possible risks to the fetus, since some medications are contraindicated during pregnancy because they are teratogenic.

Adherence to the aforementioned prevention strategies is facilitated through good monitoring and adherence to prenatal care, and allows to reduce the exposure of the pregnant woman to agents possibly harmful to pregnancy and the baby, avoiding the development and increase in the rate of CA. Later, this book will address the prevention of CA in more detail, in a specific chapter.

Congenital anomalies: how to register?

In Brazil, CA detectable at birth must be reported in the Live Birth Declaration (DNV, in Portuguese). This certificate is organized in three forms and divided into eight blocks. In field 6 of the block I, it should be filled “yes”, indicating the presence of anomalies. All visible congenital anomalies shall be described in field 41 of block VI. Each diagnosis, considering one or more anomalies, must be reported in the DNV and the Live Birth Information System (Sinasc). It is the physician's role to describe the congenital anomalies in DNV. All observed anomalies must be recorded, without hierarchy or attempt to group them into syndromes. The qualified coding of the described anomalies according to the tenth version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should preferably be performed in a second moment by people trained for this function. Therefore, the better the CA described, the better the coding work will be.[26,32]

After all, why is it important to notify?

The act of notifying a CA on the birth declaration is capable of providing a chain of events that will directly impact the individual, his family and the health system. In the individual and family spheres, the knowledge that the child has one or more abnormalities will lead to an adequate diagnosis and referral to health services for treatment, follow-up, genetic counseling and rehabilitation. In addition, it will enable the family to make choices for a future pregnancy based on information and evidence informed by the health team. Still, it can provide the call alert, with the identification of higher-than-expected incidence for the population of a certain geographical area (for example, in cases of fetal thalidomide syndrome in the 1960s and the recently occurring congenital Zika syndrome), which, in turn, makes it possible to implement different management, care and prevention measures. In the field of public health, the registration of CA allows to know the real prevalence of such diseases and can identify the need for primary, secondary and tertiary prevention strategies or policies. Although such a topic is addressed in detail in this volume, an

interesting example is the recommendation of the use of folic acid in the periconceptional period, a globally successful primary prevention strategy.[33]

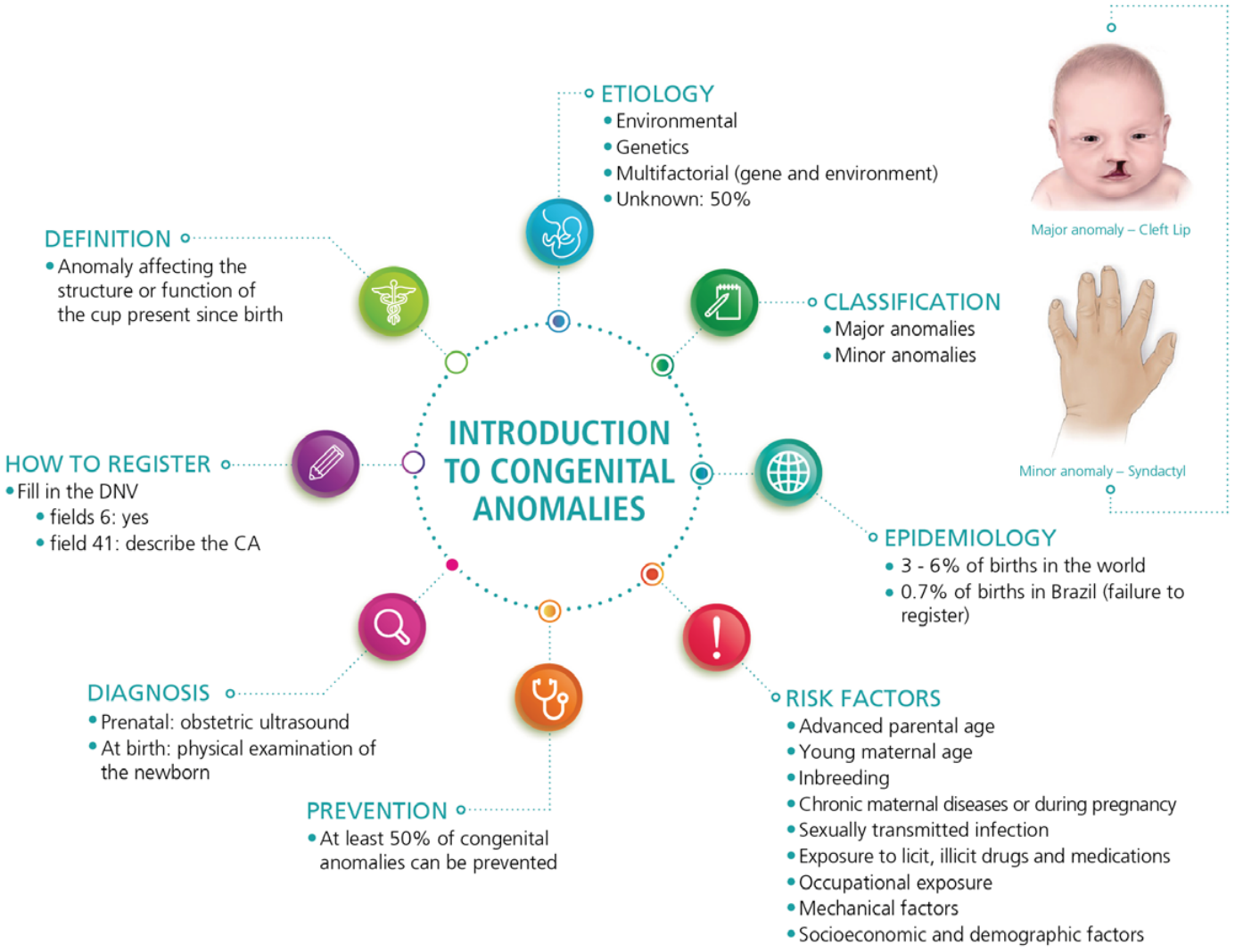
All these strategies, possible from the notification, added to the alarm of possible modifications in frequencies in space or time, in addition to the impact on the health and quality of life of the affected individual and his family, have a **social impact** directly in the population, because, as pointed out earlier, they will have an impact on public health and will allow the creation of appropriate measures for the affected populations.

Chart 2 – What you need to know about congenital anomalies (CA)

DEFINITION	Change that affects the structure or function of the body present from birth
ETIOLOGY	• Environmental • Genetic • Multifactorial (gene and environment) • Unknown: 50%
CLASSIFICATION (FIGURE 2)	• Morbidity (minor and major) • Pathogenesis (malformation, disruption, dysplasia or deformity) • Clinical presentation (isolated anomaly, sequence, multiple congenital anomaly, association or syndrome).
EPIDEMIOLOGY	3% to 6%of births in the world
RISK FACTORS	• Advanced parental age • Young maternal age • Inbreeding • Chronic maternal diseases or during pregnancy • Sexually transmitted infections • Exposure to licit, illicit drugs and medications • Occupational exposure • Mechanical factors • Socioeconomic and demographic factors
PREVENTION	At least 50% of CA can be prevented at different levels of prevention: • Primary (for example: use of folic acid) • Secondary (for example: prenatal diagnosis/ genetic counseling) • Tertiary (for example: rehabilitation)
DIAGNOSIS	• Prenatal: obstetric ultrasound, screening tests/specific diagnosis • At birth: physical examination of the newborn
HOW TO REGISTER	Fill in the Live Birth Declaration (DNV, in Portuguese) • Field 6: yes • Field 41: describe the CA

Source: authors.

INFOGRAPHIC



Source: authors. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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2 NEURAL TUBE DEFECTS

SUMMARY

OBJECTIVE

To address topics on neural tube defects (NTD), describing their formation, definitions, classification, epidemiology, management and forms of registration.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

Changes in neurulation at the time of closure in any of the portions of the neural tube produces NTD, with the phenotype varying according to the region of the neural tube that remains open. These anomalies can be classified into anencephaly, craniorachischisis, iniencephaly, encephalocele or spina bifida. Annually, 300 thousand children are born with NTD in the world and in Brazil, the prevalence of NTD reaches 24 cases per 10,000 births. Nutritional, environmental and genetic factors have already been identified as risk factors for NTD. Folic acid deficiency is the most recognized risk factor for the occurrence of NTD. However, its supplementation has shown a protective effect greater than 70% when used in the periconceptional period. Imaging tests are the main allies for the diagnosis of NTD, either in the prenatal or postnatal period. At birth, most of these anomalies can be easily recognized, but some may remain hidden. Treatment of NTD should take place in tertiary centers with trained multidisciplinary teams and the availability of multiple specialized resources. The NTD record should describe the location in the neuroaxis and whether it is open or closed. If there are other associated malformations or minor anomalies, these should also be described separately.

CONCLUSION

NTDs are conditions amenable to effective prevention and treatment, and are among the most common and serious diseases of the fetus and newborn. In this sense, they are conditions of great relevance in the field of public health and their notification should be prioritized.

KEYWORDS

Congenital abnormalities. Neural tube defects. Information systems. Surveillance in public health.

INTRODUCTION

Congenital anomalies of the neural tube closure (or neural tube defects – NTD) are among the most common and most serious diseases of fetus and newborn. Disturbance of any of the sequential events of embryonic neurulation can produce NTD, with the phenotype (e.g. anencephaly, spina bifida) varying depending on the region of the neural tube that remains open.[1] Neural tube closure has been studied for many decades, as a paradigm of embryonic morphogenesis. Neurulation is of particular interest in view of the severe congenital malformations that occur when closure fails.[2]

The objective of this chapter was to describe the occurrence of NTD in their embryological formation, characterization and classification, epidemiology, management and appropriate forms of registration.

DEFINITION

Neural tube defects (NTDs) are congenital anomalies of the brain or spinal cord that result from failure of normal neural tube closure during early pregnancy.[3] Failure of the embryonic process of closing the neural tube produces a brain and/or spinal cord in which the neural tissue is exposed to the extraembryonic environment.[1] NTDs are among the most common congenital anomalies with high prevalence around the world. In the last 100 years, the prevalence at birth of NTD has continuously decreased due to better nutrition and prenatal diagnosis with interruption of pregnancies in the countries where it is authorized.[3]

NTD inheritance patterns indicate important genetic contribution to the risk of NTD in the development of the fetus, although it is also clear that environmental factors are also important in its etiology. Open neural tube defects resulting from primary neurulation failures such as anencephaly and craniorachischisis are serious and considered lethal. Neural tube defects of the closed type, covered by skin, can range from asymptomatic, as in spina bifida occulta, to anomalies with great morbidity, in encephalocele or myelomeningocele.[4]

EMBRYOLOGY

Neurulation, which is the formation of the neural tube, is an important morphogenetic event in human development. The neural tube gives rise to the brain and spinal cord to form the central nervous system (CNS). Neurulation in mammalian embryos occurs in two phases: primary and secondary. These two phases occur in distinct areas along the rostrocaudal axis of the embryo.[5]

The so-called secondary neurulation is limited to the tail bud, which is beyond the caudal neuropore. In humans, without a tail, the tail bud is not developed as in other animals and secondary neurulation does not appear to be responsible for neural tube defects.[4]

Primary neurulation generates the entire neural tube from the rostral portion to the caudal neuropore. During this process, occurring during the third and fourth weeks of development, the flat layer of ectodermal cells that cover the notochord are transformed into a kind of hollow tube. Eighteen days after fertilization, the dorsal ectodermal midline of the embryo thickens and forms the neural plate. The neural plate first appears at the cranial end of the embryo and differs in the caudal direction. The edges of the plate thicken and begin to move upwards forming the neural fold. The neural plate becomes narrower, longer and is transformed from an elliptical structure to a keyhole-shaped structure. The development and closure of the neural tube is complete around 28 days postconception.[4]

It is noteworthy that the closure of the neural tube does not occur homogeneously, functioning as a zipper in the median region towards the ends, with some places of intersection of these closures that are common points for the occurrence of NTD.[6,7]

Multiple genes are involved in the morphogenesis of the neural tube, since many cellular processes, among them, proliferation, apoptosis and organization of the cytoskeleton are necessary for the proper formation and closure of this structure.[6,8]

CLASSIFICATION

Neural tube defects are classified in: anencephaly, craniorachischisis, iniencephaly, spina bifida and encephalocele.

Anencephaly (ICD-10:Q00.0) is the total or partial absence of the brain, or skull and skin that covers it.

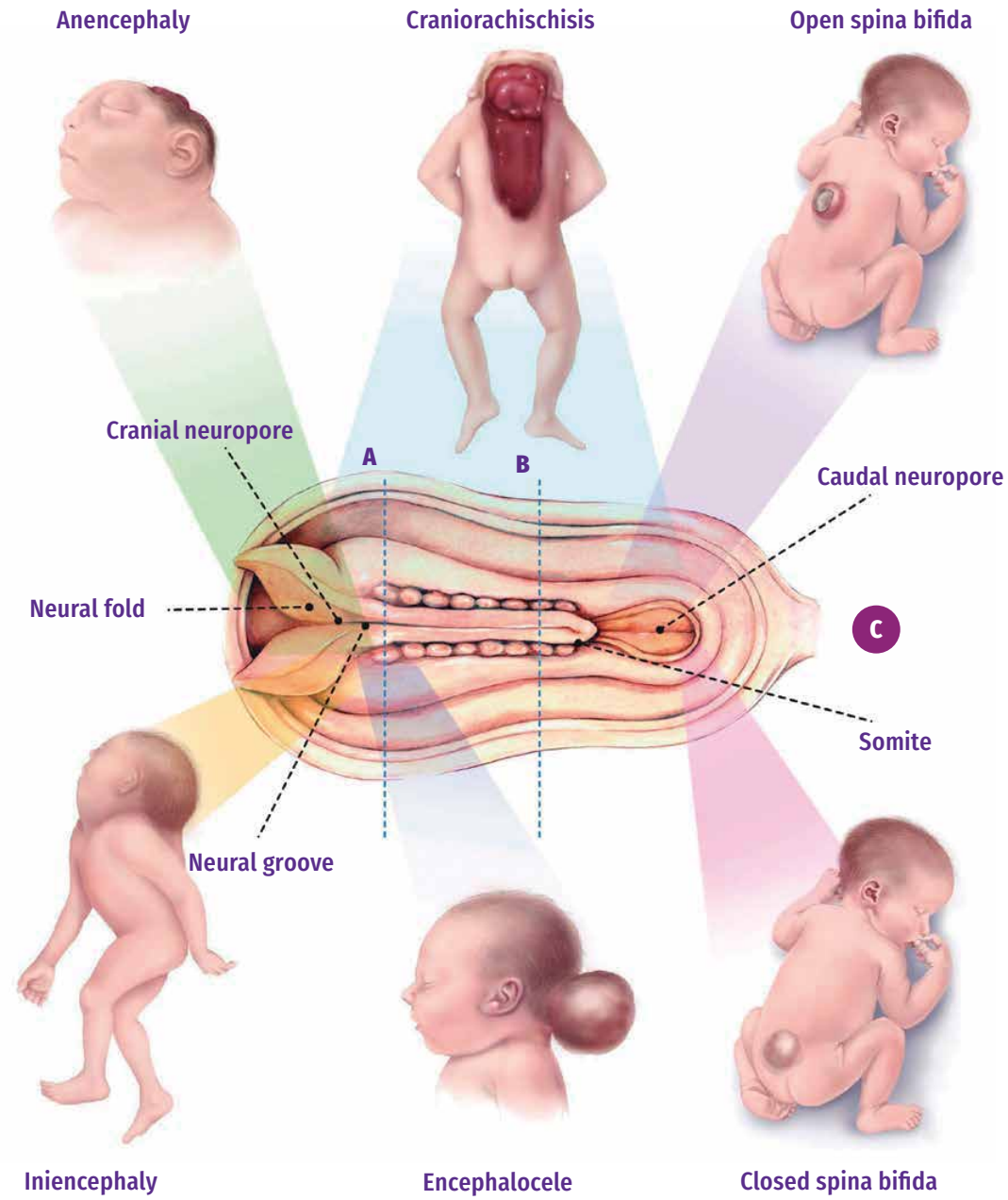
Craniorachischisis (ICD-10:Q00.1) occurs when there is anencephaly added to a bone defect of the spine, with exposure of neural tissue.

In cases of iniencephaly (ICD-10:Q00.2), rarer, there is an extreme retroflexion of the neck and trunk due to dysraphies of the occipital region.

Spina bifida (ICD-10:Q05) is characterized by herniation of the neural tissue and meninges by a bone defect of the spine. It can be open (when it is not covered by skin) or closed (when it is covered by skin), in addition, it can be cervical, thoracic, lumbar and sacral according to the region of the affected spine. Spina bifida may or may not be accompanied by hydrocephalus[9] (Figure 1).

In encephalocele (ICD-10:Q01) herniation of the brain and meninges occurs due to a bone defect of the skull, which can be frontal (opening in the frontal bone), nasofrontal (opening between the frontal and ethmoid bones), occipital (opening in the occipital bone), parietal (opening in one of the parietal bones), orbital (opening in one of the orbits) or nasal (opening in the nasal region).

Figure 1 – Classification of neural tube defects



Source: WHO; CDC; ICBDSR. **Birth defects surveillance**: atlas of selected congenital anomalies. Geneva: WHO, 2014.

EPIDEMIOLOGY

NTD contribute to infant mortality and morbidity, as well as impacting the lives of affected newborns. In poor and emerging countries, they pose an even greater challenge for the responsible health authorities. It is estimated that 1.67 per 1,000 live births present NTD, the most common being spina bifida and anencephaly. It is worth noting that the prevalence of these diseases is not equal between regions and countries, since the determining factors are variable.[10]

Annually, 300 thousand children with NTD are born in the world, of which 88 thousand die. Some studies show a large difference in prevalence between countries, ranging from 0.3 to 199.4 per 10,000 births; the lowest estimate being in Beijing and the highest in Luliang, both located in China.[11]

In Brazil, the estimated prevalence of spina bifida is 14 cases per 10,000 births; anencephaly, around 7 cases per 10,000 births; and the sum of NTDs reaches 24 per 10,000 births.[12]

RISK FACTORS

Nutritional, environmental and genetic factors have already been identified as risk factors for NTD. Folic acid deficiency is correlated with increased risk of NTD. Folic acid supplementation in the pregestational and early prenatal period has a preventive effect greater than 70% in cases of recurrence in families with a history of affected children.[13,14] In addition to folic acid deficiency, other nutritional factors have already been related to NTD, such as excess vitamin A (>15,000 IU/day)[15] and vitamin B12 deficiency.[16]

Maternal obesity is an important risk factor for NTD (RR 4.0 for women weighing >110 kg).[17,18] Diabetes disease maternal insulin-dependent (RR=15.5)[19] and hyperinsulinism (OR=1.75, 95%CI 1.09-2.82)[20] are strong risk factors and require that strict metabolic control be performed before conception so that there is a significant reduction in the incidence of NTD.

The use of teratogenic medications are recognized risk factors, in particular anticonvulsants such as carbamazepine and valproic acid.[13] Drugs that interfere with the metabolism or absorption of folic acid (such as sulfamethoxazole-trimethoprim, methotrexate, sulfadoxin-pyrimethamine, azathioprine, among others)[21] and retinoic acid have a well-established effect on the occurrence of NTD.[22]

Genetic changes have an impact on the development of NTD, being greater in female fetuses, in consanguineous couple children and in several genetic syndromes (e.g. Meckel syndrome).[23] To date, no correlation of increased risk of NTD and variants or polymorphisms in the gene has been identified *MTHFR* (involved in folate metabolism).[24]

PREVENTION

Folic acid allows the primary prevention of NTDs, a recommendation established by the Medical Research Council (MRC) in a study that identified a recurrence rate of NTDs of 1.0% in the supplemented group and 3.5% in the control group (RR=0.28), with a preventive effect of 72%.[14] Subsequently, it was found that multivitamin supplementation (containing folic acid) also prevents the primary occurrence of NTDs.[25] Currently, some countries have mandatory fortification in staple foods (e.g. wheat flour), demonstrating variable association in the level of risk reduction in different regions.[12,26]

The current recommendation for the prevention of the first occurrence of NTD is the maternal use of 400 µg of folic acid, orally, once daily, at least four weeks (one month) before conception until the 12th week of gestation. In the prevention of recurrence of NTD, larger doses are recommended (>4 mg), for the same period. The commercial availability of folic acid at a dose of 5 mg proved to be an effective option, with no evidence of adverse effects or contraindications in these dosages.[27] Other situations in which higher dose is also recommended are: parent(s) with dysraphism/NTD (including attenuated forms), use of anticonvulsants during pregnancy, diabetes disease, celiac disease (or other malabsorption states), sickle cell anemia, and previous family history of NTD.[28] In addition, it is important to emphasize that the mitigation of risk factors previously described through women's health care in the preconception and prenatal period are fundamental for prevention.

This book has a specific chapter that presents in more detail the prevention of congenital anomalies.

DIAGNOSIS

Prenatal diagnosis is performed by ultrasound (US). In the presence of ultrasound abnormalities, research for associated abnormalities, genetic tests and fetal magnetic resonance imaging may be recommended. CNS structures can be identified by US at different gestational ages (GA): skull, midline and sickle from 12-14 weeks; spine from 12-14 weeks (preferably 19-21 weeks); cerebellum from 19-21 weeks; corpus callosum, gyros and grooves after 28 gestational weeks. Thus, prenatal diagnosis of anencephaly can be performed in the 1st trimester, spina bifida in the 2nd trimester (through the evaluation of morphological ultrasound, when performed) and corpus callosum agenesis only in the 3rd trimester.[29] Updated guidelines on prenatal screening, diagnosis and management in pregnancy of NTDs can be obtained in another publication.[29]

The postnatal diagnosis of open NTD is usually obvious at birth due to the visible lesion. Myelomeningocele (spina bifida) is the most common defect of the neural tube, characterized by a raw, red and fleshy plaque, seen by the defect in the spine and skin, with a protruding membranous sac containing meninges, cerebrospinal fluid (CSF) and nerve roots, which protrude through the defect.[30] In approximately 80% of cases, the vertebral defect involves the lumbar and sacral region.[31] The best clinical characterization of the lesions subsequently requires the performance of complementary imaging examinations (such as X-rays, tomography and magnetic resonance imaging), which will indicate the degree of impairment, topography and associated anomalies.

TREATMENT

Prenatal management, when there is a diagnosis still in the gestational phase, includes a discussion with parents about the natural history of the disease, the offer of additional prenatal tests, the choice of service and delivery route and, when applicable, the possibility of performing fetal surgery[i]. In this period, it is also possible to address issues of postnatal treatment (surgical procedures, possibility of ventriculoperitoneal shunt (VPS) and prognosis), reinforcing the importance of prenatal diagnosis in the best management of these patients.

The safety and efficacy of fetal surgery on NTDs (myelomeningocele) were evaluated in the study conducted by Adizik and collaborators,[32] which demonstrated efficacy and good results of this procedure, including: lower need for VPS, better motor and cognitive outcomes, possible improvement in bladder function, and improvements in quality of life. The risks of this procedure reported were premature birth, chorioamnionitis, premature rupture of amniotic membrane, oligohydramnios, among others.

In these cases, it is recommended that childbirth should always take place in hospitals with neonatal intensive care unit (ICU), neurosurgery services and multidisciplinary team qualified for the specific needs of these patients (for example, gloves and latex-free equipment due to the high risk of latex allergy).[33,34] Full-term delivery is preferable, but increased ventriculomegaly with macrocephaly in US may require premature delivery and often by cesarean section. In the delivery room, one should observe the location and size of the lesion and whether there is CSF leakage[35] then the defect is covered with a sterile dressing soaked in saline solution, with the newborn (NB) in ventral or lateral decubitus to avoid prolonged pressure on the lesion. Complete neurological examination should be performed in these patients, to identify deficits, and supplemented with imaging examination to assess associated changes (such as hydrocephalus and compression of the brainstem).

The investigation and documentation of associated anomalies (e.g. crooked feet, contractures, hip dysplasia) is essential, as is the evaluation of urinary pathways that often present malformations and functional alterations. Broad-spectrum antibiotic prophylaxis should be administered until surgical correction (NTD closure), which should be performed within the first 72 hours of life to reduce the risk of CNS infection. Complications of closure include CSF leakage, infection, dermoid inclusion tumors and, especially, development of some degree of hydrocephalus – which requires serial measurement of the head circumference and the size of the ventricles (verified by US), in order to determine the need for VPS placement.[33,35]

Multidisciplinary follow-up is essential and should include several medical specialties (neurologists, nephrologists, urologists, neurosurgeons, pediatricians and clinical geneticists) and other health professionals (physiotherapist, nutritionist and occupational therapist), due to

[i] Fetal surgery, although it still has several limitations, especially for its offer, already presents quite promising results in terms of neurological prognosis. It is a procedure performed only in specialized centers that have multidisciplinary teams qualified in the technique. In SUS, this procedure is not available, only in the context of specific experimental projects for the evaluation of this new technique.

the high risk of comorbidities that may occur in patients with NTD. Among these complications, for example, are: obesity/overweight (due to reduced mobility), urinary infections and kidney failure (problems with sphincter control), scoliosis and deformities of the rib cage (due to poor posture and loss of muscle mass) and seizures (sequelae of severe hydrocephalus).

The various clinical manifestations and complications associated with this condition can significantly interfere with the various components of the quality of life of patients and their family nucleus, and the multidisciplinary approach is of great importance to promote the physical, psychological and social well-being of these patients.[36]

HOW TO REGISTER?

For the registration of the neural tube defect in the live birth declaration (DNV, in Portuguese), the location of the defect along the neuroaxis is described. It is important to identify whether the defect is open or closed. Define whether the contents of the neural tube are exposed to the environment, covered by the meninges or by the whole skin. When there is doubt of which term to use, in addition to the description, a simple and schematic drawing can be made that helps in understanding. Other malformations may be associated and should also be recorded, as they will later be coded and accounted for epidemiological purposes separately. Minor anomalies identified by the physical examination of the NB should be included, such as sacral dimples, unusual pilification and skin changes. It is recommended to prioritize simple and easy-to-understand language to avoid naming errors. Some malformations can cause confusion among themselves, such as encephalocele and meningocele, so it is suggested to always review the definition in these cases and seek a detailed description.[9,37]

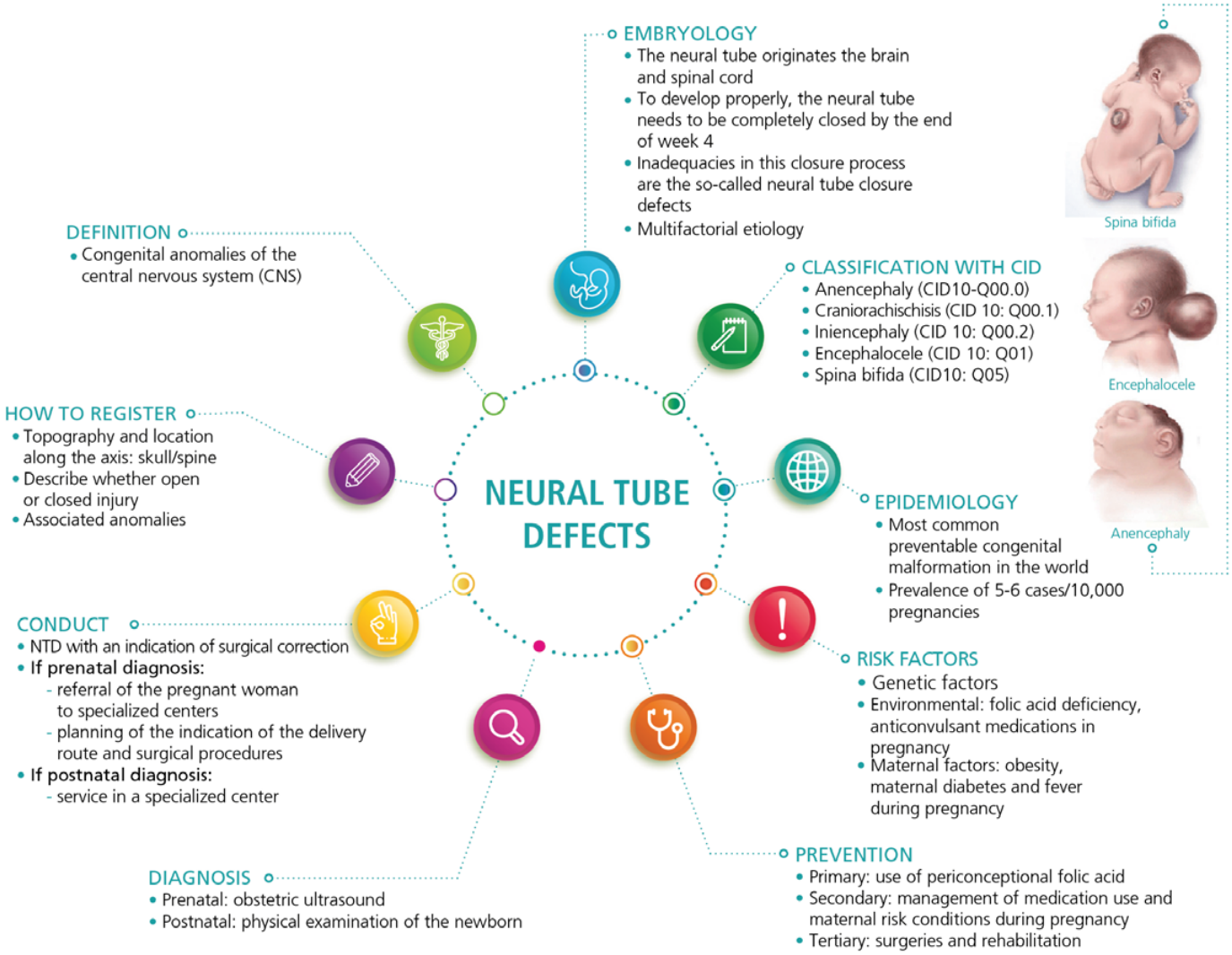
FINAL CONSIDERATIONS

The multifactorial etiological complexity of NTDs represents a challenge in the analysis of population studies and genomic predictors, that is, it is difficult to determine the association between genetic markers and the occurrence of these malformations.[38] Researchers need to integrate genetic data with information on epigenetics and environmental factors for the global elucidation of the cause of each NTD individually.[39] Food fortification with folic acid represents a major advance in public health in reducing the risk of NTD, however, this group of defects remains one of the most common globally. Due to the heterogeneity of NTDs it is believed that multiple interventions in primary prevention can further reduce this risk. The clinical severity, the etiological uncertainty, as well as the advance in the technical capacities of identification and studies, make NTD an international priority for future research. Surveillance initiatives are expanding and are essential for evolution in appropriate prevention and intervention.[40]

TO REMEMBER

- NTDs are common, have a high impact on infant mortality and morbidity and can be preventable; therefore, it is extremely important to do surveillance and thus be able to prevent them.
- The main types of NTD are anencephaly, craniorachischisis, encephalocele, spina bifida and iniencephaly, the most frequent being spina bifida and anencephaly.
- Folic acid deficiency is an important risk factor for the occurrence of NTD, with its supplementation demonstrating a protective effect greater than 70%, when used in the periconceptional period.
- The current recommendation for the prevention of the first occurrence of NTD is the use 400 µg folic acid orally once daily at least four weeks (one month) before conception until the 12th week of gestation. In the prevention of recurrence of NTD, larger doses are recommended (>4 mg), for the same period.
- Prenatal diagnosis of the different NTDs can be done by means of ultrasound, according to gestational age; being an important measure for planning the pre and postnatal management of these conditions.
- Clinical examination and imaging examinations allow the diagnostic establishment of NTD, as well as the degree of impairment, topography and associated anomalies, fundamental in the conduct subsequently.
- Treatment of NTDs should take place in tertiary centers with trained multidisciplinary teams and availability of neonatal ICU, neurosurgery service and specialized imaging examinations.
- The NTD record should describe the location in the neuroaxis, whether it is open or closed (exposed or covered by meninges or skin), and when the presence of other malformations or associated minor anomalies, these should also be described.

INFOGRAPHIC



Source: authors. Infographic/images - WHO/CDC/ICBD. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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GLOSSARY

Anencephaly: complete or partial absence of the brain. There may be absence of cranial vault (ACRANIA) and skin covering the brain.

Craniorachischisis: anencephaly associated with a continuous defect of the spinal cord, without coverage of meninges. It can occur limited to the cervical region or affect the entire spinal cord.

Encephalocele: it is a cystic lesion with protrusion from a defect in the skull.

Spina bifida: neural tube defect in the spinal cord with protrusion of components in the spine.

Hydrocephalus: accumulation of the excessive amount of fluid that causes dilation of the cerebral ventricles and/or increased intracranial pressure.

Iniencephaly: a complex defect that involves the occipital region of the skull and the medulla, resulting in retroflection of the head.

Meningocele: type of spina bifida in exteriorization of the meninges occurs.

Meningomyelocele: type of spina bifida in which exteriorization of meninges and portions of the spinal cord occurs.

Myelocele: type of spina bifida in which exteriorization of the spinal cord occurs.

Caudal neuropore: lower opening of the neural tube.

Rostral neuropore: upper (cranial) opening of the neural tube.

Neurulation: embryonic period in which the formation of the neural tube occurs, a structure that will give rise to the Central Nervous System (CNS).

3 CONGENITAL MICROCEPHALY

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SUMMARY

OBJECTIVE

To address the different causes of congenital microcephaly, the associated risk factors, prevention strategies, as well as guidelines on its correct notification in the Live Birth Declaration (DNV, in Portuguese).

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

The term, microcephaly refers to a measure of lower head circumference relative to the average in the general population, adjusted for sex and age. This decrease in cranial circumference is usually secondary to brain damage that may have genetic, environmental, or a combination of both factors. For the purposes of surveillance of congenital Zika syndrome, the value of two standard deviations below the mean was chosen as a threshold for investigation, however other symptoms and findings may be associated. However, the Live Birth Information System (Sinasc) records severe microcephaly, which is defined by a threshold of three standard deviations below the average.

CONCLUSION

Microcephaly is a congenital anomaly that can present itself in severe form, associated with neurological complications, intellectual development delay, sensory changes and even cerebral palsy. Microcephaly gained great notoriety in the country in its epidemic, in the years 2015 and 2016. In this sense, this condition has great relevance in the field of Public Health in Brazil and its notification should be prioritized.

KEYWORDS

Congenital abnormalities. Microcephaly. Zika virus infection. Information systems. Surveillance in public health.

INTRODUCTION

During the years of 2015 and 2016, an outbreak of children born with microcephaly reached Brazil and later other countries in Latin America. Very quickly the association between microcephaly and prenatal infection by the Zika virus was established.[1,2] Microcephaly is defined by a head circumference (HC) below two standard deviations from the mean for gestational age and sex, and severe microcephaly is defined as below three standard deviations. Although it is an anthropometric definition, severe microcephaly usually reflects the decrease in brain size and is an important predictor of neurological dysfunctions in the future of the child.[3] Although severe microcephaly is associated with neurological complications such as epilepsy, intellectual development delay, sensory changes (vision and hearing) and even cerebral palsy, milder microcephaly can have a good prognosis or even a normal development.[4]

CLASSIFICATIONS

Microcephaly is classified as primary, when it is due to a change in neurogenesis (mitosis or progenitor cell function) or death of neuronal progenitors and is present at birth (congenital). Secondary microcephaly is of appearance after birth, when the brain does not grow according to the expected curve and is usually related to problems in the development and postnatal maturation of neurons (dendritic processes and synaptic connections).[5]

Another important classification of microcephaly is whether it presents as an isolated defect or associated with abnormalities in organs or systems other than the Central Nervous System (CNS) and, in this case, genetic syndromes should always be investigated. It is also important to observe whether the size of the head is symmetrical in relation to the face and body of the child or asymmetrical, in which the skull is much smaller than the face and the rest of the body and with changed shape. The so-called microcephaly vera is a situation where the size of the brain is decreased evenly and without evidence of injury or brain injury. This type of microcephaly usually has autosomal recessive inheritance and is the result of a widespread problem in the cell cycle and the growth of neural precursor cells.[5] On the other hand, in many cases of microcephaly underlying CNS abnormalities are found, such as microcephaly caused by congenital infections, including congenital Zika syndrome (CZS).[6]

CAUSES AND FACTORS ASSOCIATED WITH CONGENITAL MICROCEPHALY

Microcephaly can have both genetic causes (chromosomal abnormalities and gene changes), environmental (congenital infections) or have multifactorial etiology, in which genetic susceptibility and environmental risk factors are summed The main genetic causes and environmental risk factors associated with the occurrence of microcephaly are presented in Charts 1 and 2, respectively.

Of the genetic causes we draw attention to some frequent chromosomal syndromes, such as Down syndrome and other numerical anomalies that, in turn, are more frequent with the advancement of maternal age at the time of pregnancy and can be diagnosed by karyotype. A series of gene changes follow, in which the karyotype is normal and the diagnosis starts from a hypothesis made from a careful clinical examination associated with family history. The diagnosis of confirmation of etiology in gene syndromes is made by DNA analysis (molecular tests) that also allow an adequate genetic counseling.[7,8]

Chart 1 – Main genetic causes of microcephaly

TYPE	CAUSES
Numerical chromosomal abnormalities:	Trisomies 13, 18, 21
Microdeletion and/or microduplication syndromes	4p Wolf-Hirschhorn Deletion 5p Cri-du-chat Deletion 22q11 Deletion 17p13.3 Deletion 3q29 Duplication 17q21.31 Duplication Xq28 Duplication Other deletions or duplications
Monogenic **Note:** this list would be very extensive by the number of genetic syndromes with microcephaly. Therefore, we selected the ones most often found in the clinic.	Autosomal recessive microcephaly Seckel Syndrome Aicardi-Goutieres Syndrome Cockayne Syndrome Cornelia de Lange Syndrome Rubinstein-Taybi Syndrome Rett Syndrome Smith-Lemli-Opitz Syndrome Craniosynostosis Syndromes
Metabolic causes (innate errors of metabolism)	Deficiency in serine biosynthesis Deficiency in sterol biosynthesis Mitochondriopathy Congenital defects of glycosylation syndrome
Congenital anomalies of multifactorial causes	Anencephaly (which can be confused with very severe microcephaly) Holoprosencephaly

Source: authors.

In environmental factors, prenatal infection by Zika virus brought to the agenda the impact of infectious diseases on the Central Nervous System of a developing fetus, but for a long time the infections of the STORCH group (syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes) and HIV have already been associated with primary or secondary microcephaly. Rubella is already eradicated in Brazil thanks to vaccination schedule associated with campaigns for vulnerable groups since the 2000s. On the other hand, HIV, syphilis, toxoplasmosis and cytomegalovirus have high prevalence in Brazil.[9]

Chart 2 – Maternal risk factors for primary microcephaly (prenatal)

TYPE	RISK FACTORS BY GROUPS
More frequent teratogenic exposures	Alcohol consumption (safety of low doses is unknown) Tobacco Therapeutic radiation (diagnostic procedures do not present this risk) Some medications Exposure to lead, organic mercury and toluene
Chronic diseases and conditions	Untreated maternal phenylketonuria Poorly controlled diabetes Severe gestational hypertension Poorly controlled maternal hypothyroidism Folate deficiency Malnutrition Placental insufficiency
Infections	STORCH+Z: syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, Zika virus HIV

Source: authors.

Among the non-infectious causes, other treatable maternal diseases are noteworthy for their frequency and for the possibility of treatment and primary prevention when diagnosed early, such as hypothyroidism, diabetes and hypertension (Chart 2). Finally, we draw attention to the consumption of alcoholic beverages during pregnancy as one of the most prevalent causes of intellectual disability in the Western world. Although severe microcephaly is rare, alcohol consumption even in moderate doses can cause a decrease in the head circumference associated with neurobehavioral disorders.[10]

PREVALENCE IN LIVE BIRTHS

Detailed aspects of prevalence and epidemiology were addressed in specific chapters. Severe microcephaly is a rare condition that before the Zika virus epidemic, was estimated at a baseline of 3/10.000 live births in Latin America[11], two times higher than recorded in Europe (1.5/10,000).[12]

HOW TO IDENTIFY CONGENITAL MICROCEPHALY

The measurement of the head circumference should be made with a non-extensible tape measure, at the height of the supraorbital arches, anteriorly, and the greater prominence of the occipital bone, posteriorly (Figure 1).[13] The values obtained should be recorded in charts of cranial growth, which allow the construction of the curve of each child and the comparison with the reference values. The measurement of the skull should ideally be carried out in the delivery room and repeated 24 hours after birth. One of the major issues in the classification of the head circumference is the curve that will be used to reference the measurement found in that individual, since population characteristics must also be considered. Thus, currently, the use of INTERGROWTH-21 curves is the most appropriate, since they consider gestational age at birth and include Brazilian children in their elaboration.[14]

Figure 1 – Standardized technique for head circumference measurement

Source: Brasil, 2015.[15]

Measurement Guidelines: use an inelastic tape measure. Place on the most prominent point of the back of the skull (occipital) and on the eyebrows. If there is any front protrusion and it is asymmetrical, pass the tape measure over the most prominent part.

DIAGNOSTIC EVALUATION OF CONGENITAL MICROCEPHALY

The detailed assessment and etiological diagnosis of microcephaly are extremely important for determining the underlying cause, which, when known, allows the identification of possible associated conditions, prognosis and appropriate management. Identifying risk factors or genetic

causes can also prevent the birth of other affected children in the same family.

Detailed gestational and family history is essential, accompanied by a survey aimed at identifying chronic or acute maternal diseases, including signs of infection, fever, and medication use. The occupation of work and place of residence may also indicate environmental risks. Inbreeding increases the likelihood of microcephaly of recessive and even multifactorial etiology. Inbreeding should be investigated not only by asking about the kinship between parents, but also their place of birth, religion and ancestry. Often in small and isolated locations, as well as ethnic and religious groups that remain isolated, there is a greater likelihood of inbreeding. In population genetics, we call endocrinization, or marriages preferably within a group, which can be geographical, cultural or religious.[16]

Clinical examination should be directed to the presence of other associated external anomalies and to the observation of the presence or not of growth restriction. Careful cardiac auscultation and eventual echocardiography is very important, especially when microcephaly is accompanied by abnormalities in other organs or systems. Palpation of the liver and spleen helps identify hepatosplenomegaly, present in many congenital infections. This clinical examination should be complemented by audiological and ophthalmological evaluation with special attention to the fundus, as well as directed at possible conditions associated with microcephaly, such as epilepsy and cerebral palsy.

Imaging tests are very useful, as they can identify brain structural abnormalities (brain magnetic resonance imaging, transfontanellar ultrasound, and skull CT). The types of anomalies present and observed in these imaging tests are important indicators of both prognosis and auxiliary in etiological diagnosis. For example, congenital infections are often associated with intracranial calcifications.[17]

As for laboratory tests, the performance of STORCH tests on the baby and the mother immediately after birth, is fundamental and should include the test for cytomegalovirus and Zika virus. The detection of IgM antibodies in the newborn is an important indication of fetal infection, but over time it loses its sensitivity (since IgM is short-lived), as well as specificity (since the baby can contract infections in the postnatal period). For the diagnosis of cytomegalovirus infection, the search for the virus in the urine in the first months of life is the gold standard.[18]

KARYOTYPE/GENETIC TESTING

In all cases where microcephaly is associated with other structural anomalies of organs or systems, karyotype should be performed. More specific genetic tests may be requested after clinical evaluation, leading to the suspicion of some syndrome and the environmental causes excluded.[17]

Prenatal diagnosis can be performed by obstetric ultrasound, but although CNS structures can be identified by this technique at different gestational ages, microcephaly is not usually recognized until the third gestational trimester.[19]

TREATMENT

Treatment is directed to the consequences or conditions associated with microcephaly and includes multi-professional staff. In severe microcephaly cerebral palsy is common, and treatment should include physiotherapy and supportive treatments for hypertonia and swallowing problems. Since epilepsy is very common, it is important to guide parents and caregivers for the recognition of signs of crises. Early stimulation is fundamental in neurocognitive and motor development.

PREVENTION MEASURES

Primary prevention measures can be both at the individual and population level. Because there is no specific treatment for microcephaly, its prevention is the best measure and ideally should be carried out in programs that include a significant fraction of the population and women of reproductive age. Pregnancy planning is ideal, but we know that almost 50% of pregnancies are unplanned.[20] Therefore, general measures are important even if they are not targeted specifically for pregnant women, such as diabetes control, weight control, flour fortification with folic acid, responsible alcohol consumption, tobacco abstinence, vaccination programs and control of transmitting mosquitoes, for example, can be very effective in reducing risks in unplanned pregnancies. Details can be found in the chapter dedicated to the Prevention of congenital anomalies.

In pregnancy, starting prenatal care preferably before the 12th week is essential to identify risk factors and to follow-up during pregnancy, favoring appropriate actions and interventions that avoid complications and protect women's health. It is also important to be attentive to the guidelines, the behaviors and the risk classification in prenatal care. If any changes are identified that indicate referring the pregnant woman to high-risk prenatal care, the service network should be activated in order to prioritize their care.[13]

In general, pregnant women should be guided about the need for attention to the nature and quality of what is ingested (liquids, foods, supplements), and the potential of these products to affect the development of the baby.

Also during prenatal care, one should investigate and guide about used medications, exposure to toxic substances and the use of tobacco, alcohol and other drugs. It is important to reinforce that the ideal is total abstinence from alcohol during pregnancy and breastfeeding, since even moderate doses of alcohol are associated with neurobehavioral changes, even in the absence of microcephaly.

In the STORCH infection, the strategies vary, there is a vaccine for rubella and the disease is eliminated from Brazil, toxoplasmosis, and syphilis do not have a vaccine, but the diagnosis of pregnancy allows for effective treatment of both the mother and the fetus during pregnancy; cytomegalovirus does not have a vaccine, and the adoption of good hygiene is the best strategy

to prevent it, Zika relies on measures of personal protection against mosquito bites, and environmental measures to prevent the proliferation of these insect vectors. Finally, it also includes guidance on the use of condoms in all sexual relations for the prevention of sexually transmitted infections and vertical transmission of HIV, syphilis, viral hepatitis and Zika.

This book has a specific chapter that presents in more detail the prevention of congenital anomalies.

HOW TO REGISTER?

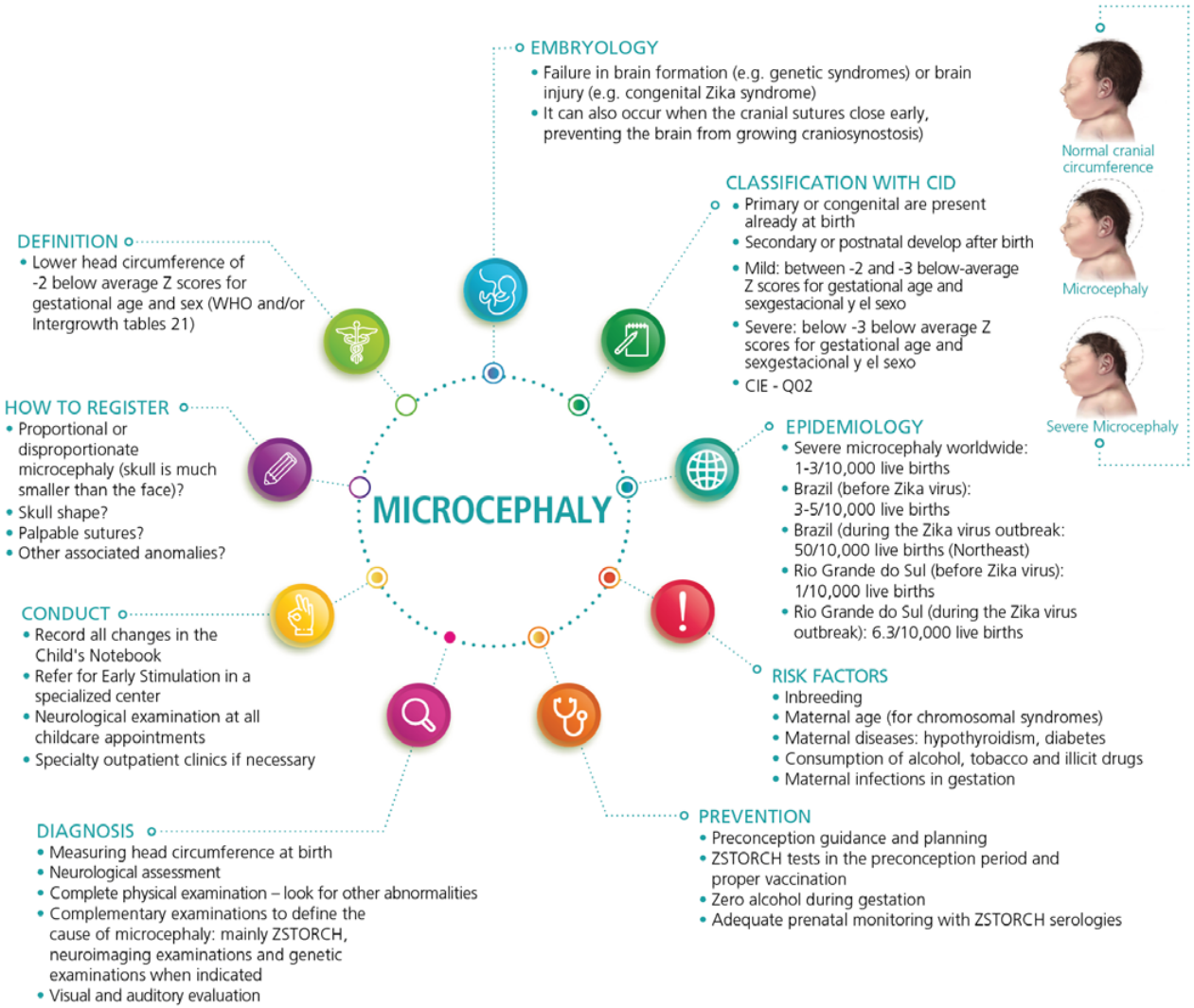
The proper registration of microcephaly cases is of fundamental importance for the subsequent diagnostic evaluation and conduct. The code assigned to this malformation is ICD-10:Q02. When other malformations are present, they must be fully recorded. It is important to reinforce that in Sinasc only severe microcephaly should be recorded (head circumference less than three standard deviations below the mean). Mild microcephaly will be reported in Sinasc only if accompanied by obvious brain or neurological abnormalities.[13] Anomalies such as anencephaly and encephalocele even if they have decreased head circumference should be recorded with their own code (Q00 and Q01, respectively).

In addition to the Sinasc, as of November 2015, due to the health emergency by the increase in cases of microcephaly, and the Ministry of Health of Brazil, has developed an electronic instrument,, online, called the Record of Events in Public Health microcephaly (RESP-microcephaly), built at the Department of Informatics of the Unified Health System (DataSUS), to carry out the notification, then the tracking, search, sort, and with the final diagnosis of new cases of microcephaly.[15]

TO REMEMBER

- Microcephaly is a sign, not a diagnosis.
- Microcephaly can have many causes.
- Always remember congenital infections and look for other associated anomalies.
- Alcohol is an important teratogen: it can cause microcephaly and problems in neurological and behavioral development even when the head circumference is normal.
- Frequently used medications during pregnancy that can cause microcephaly are among some types of anticonvulsants such as valproic acid and hydantoin, and oral isotretinoin.
- For specific information on teratogens see the National Information System on Teratogenic Agents (Siat) – Safe Pregnancy (www.gravidezsegura.org).

INFOGRAPHIC



Source: authors. Infographic/images - WHO/CDC/ICBD. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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4 CONGENITAL HEART DISEASES

SUMMARY

OBJECTIVE
To review the detection of congenital heart disease (CHD) in the prenatal period, at birth and postnatal period, and facilitate adequate registration.

METHODS
Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS
CHD are the most common congenital anomalies among newborns. The main risk factors related to the origin of CHD were reviewed, mainly maternal and fetal conditions, in addition to classification, characteristics of diagnosis, management, registration and prevention.

CONCLUSION
Cardiac anomalies are defects that require specialized surgical procedures. Prenatal and neonatal diagnosis increases the chances of survival and decreases morbidity.

KEYWORDS
Congenital abnormalities. Congenital heart disease. Information systems. Surveillance in public health. Birth declaration.

INTRODUCTION

The heart is the first organ to function in the human embryo, around the fourth week of gestation.[1] Congenital heart disease (CHD) is the most common kind of congenital anomaly, occurring in approximately 4 to 50 per 1,000 live births and approximately 1 in 10 stillbirths.[2,3] Several genetic syndromes are associated with CHD, with chromosomal abnormalities present in approximately 20% of these heart diseases.[4] When detected in prenatal care, they may have a better outcome, both in terms of mortality, morbidity and quality of life, since most of them will require surgical procedures even in the neonatal period and in the first year of life.[5] The objective of this chapter is to review the detection of CHD in the prenatal period, at birth and postnatal, and facilitate adequate registration.

RISK FACTORS FOR CONGENITAL HEART DISEASE

Several maternal conditions increase the risk of congenital heart disease. Maternal conditions can be present before pregnancy such as diabetes and collagenosis or acquired during pregnancy such as viral, bacterial and parasitic infections. In addition, exposure to medicines, licit and illicit drugs may also predispose to the development of congenital heart disease, as listed in Charts 1 and 2.[6] There are also fetal changes that, once present, indicate frequently to the presence of CHD. Among the viral infections, rubella stands out, which can lead to hypoplasia of the pulmonary artery and persistence of the arterial duct, among other congenital problems.[7]

Chart 1 – Maternal risk factors for congenital heart diseases

METABOLIC DISEASES	Diabetes *Mellitus*
COLLAGENOSES	Systemic Lupus Erythematosus Rheumatoid arthritis
EXPOSURE TO TERATOGENIC AGENTS	Alcohol Smoking Drugs with action on the CNS
USE OF MEDICATIONS DURING GESTATION	Indomethacin Aspirin Carbamazepine Phenytoin Valproic acid Others
INFECTIONS	Turn Parasitic
PERSONAL AND FAMILY BACKGROUND	Maternal and family risk factors Advanced maternal age Previous fetal losses

Source: authors.
Note: CNS – Central Nervous System.

Chart 2 – Fetal risk factors for congenital heart disease

	EXTRACARDIAC ABNORMALITIES DETECTED ON OBSTETRIC ULTRASOUND
Fetal changes	Increased nuchal translucency in the 1st trimester Oligohydramnios Polyhydramnios Intrauterine growth retardation Non-immune fetal dropsy Presence of changes in heart rhythm

Source: authors.

Advanced maternal age, considered from 35 years of age, is associated with increased risk of chromosomal changes such as trisomy of 13 (Patau syndrome), 18 (Edwards syndrome) and 21 (Down syndrome). All three conditions have a high prevalence of congenital heart disease of different severity.[8] For example, 40%-50% of children with Down syndrome have CHD and this can be decisive in the prognosis of survival and development.[9]

CLASSIFICATION OF CONGENITAL HEART DISEASE BY SEVERITY

CHD can be classified according to their severity and the period in which they will need intervention, as shown in Chart 3. They are considered critical heart diseases to those that will need procedures still in the neonatal period, they are also called dependent on the arterial canal to supply the flow for systemic or pulmonary circulation. Severe congenital heart disease should undergo intervention in the first year of life. There are also significant congenital heart diseases that persist for more than six months and cannot be classified in the previous categories.[10]

Chart 3 – Classification of congenital heart diseases according to severity and need for procedures

HEART DISEASE	PERIOD OF PROCEEDINGS	EXAMPLES
Critical	Neonatal	Coarctation of the critical aorta Critical pulmonary stenosis Transposition of large vessels Total pulmonary anomalous venous drainage Univentricular dependent on the ductus arteriosus
Severe	First year of life	Interventricular Communication Tetralogy of Fallot Interatrial communication Defect of the atrioventricular septum Partial pulmonary anomalous venous drainage Truncus arterious Anomalous origin of coronary
Significant	Lifetime	Patent oval foramen Bicuspid aortic valve

Source: authors.

PRENATAL DIAGNOSIS OF CONGENITAL HEART DISEASE

There are some maternal and fetal conditions that are associated with increased risk of CHD as mentioned earlier. Thus, when there are maternal risk factors for suspected congenital heart disease, complementary examinations may be requested, including imaging tests such as morphological ultrasound. This should be performed around the 20th week of gestation, emphasizing that the optimal time would be between 24 and 28 weeks. For pregnant women at risk, however, a transvaginal echocardiography at 14 weeks of gestational age is recommended, especially for those whose first trimester screening was indicative of cardiac abnormality. This procedure, however, is not yet a routine yet in Brazil during prenatal care.[11]

DIAGNOSIS AT BIRTH

Critical and severe heart diseases are possible to be detected in the first 48 hours of life through the heart test (teste do coraçãozinho) and clinical examination. Physical examination of the newborn should be performed at birth and at hospital discharge in search of heart murmur. We must also pay attention to signs of defects of the right side of the heart such as cyanosis, hepatomegaly, edema of the lower limbs, respiratory distress and moaning; as well as signs of defects of the left side such as tachypnea, hyperdynamic precordium, galloping rhythm, third bulla, differential of pulses and pressure and shock. In addition to the physical examination, the heart test should be done, which, in Brazil, was made mandatory in all maternity hospitals. Since it lends itself mainly to the detection of critical heart diseases, that is, whose defects depend on the patency of the arterial canal to maintain pulmonary or systemic flow, the closer to hospital discharge, the greater the chance that some change is detected. It is a test that evaluates the difference in pulse oximetry between the right upper limb and the lower limb, and also whether the overall oxygenation of the newborn is outside the normal. There are clinical situations that alter this test, leading to false-positive results, such as neonatal sepsis and respiratory failure. Thus, if the test is positive, a confirmatory doppler echocardiography should be performed.[12,13]

If newborns require hospitalization in the neonatal treatment unit in the first 48 hours of life, one should not fail to perform both the heart test and pay attention to the cardiological physical examination mentioned earlier.

There are clinical situations suspected of cardiac alteration in the neonatal period: unexplained shock and cyanosis, newborns with syndromic diagnoses such as Down, Di George and Turner, who have other major extracardiac malformations, who have a chest radiogram with little or no pulmonary vasculature or who, on the other hand, have congestion and cardiomegaly; who have an electrocardiogram (ECG) with atrial or ventricular overload or who also have a change in the hyperoxia test.[13]

INITIAL HANDLING

The initial management of the newborn with suspected critical CHD concerns the maintenance of patency of the ductus arteriosus with prostaglandin infusion, restriction of oxygen therapy and decrease of nociceptive stimuli for subsequent confirmation with doppler echocardiography.

If the diagnosis of severe CHD is not performed in the prenatal or neonatal period, the children will develop a progressive picture of cyanosis or heart failure such as digital drugging, low weight gain, gagging, difficulty breastfeeding, repeated respiratory infections, shock, cardiac arrest and death. Important to exclude CHD in frames of this type in differential diagnosis.

HOW TO REGISTER?

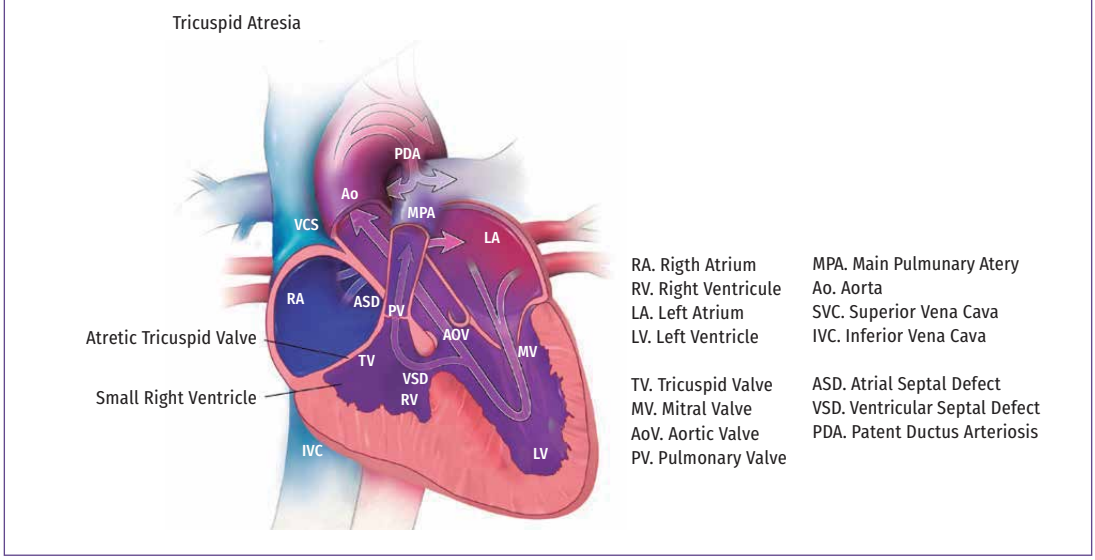
The registration of congenital heart disease should follow its morphological classification, as shown in the illustrations below. As already mentioned in this and other chapters, it is the detection, followed by an appropriate registration, that will allow timely therapeutic actions, as well as subsequent preventive actions and, when necessary, also genetic counseling. Such actions include from the initial management to referral to reference centers, through the guidance of parents for the next pregnancies.

Hereafter, CHD and the corresponding possible ICDs are listed. Defects can be characterized as hypoplasia of the ventricles, stenosis of the large vessels, exchange of the large vessels, and communications between the atria and the ventricles or both.

The so-called univentricular heart diseases are generally not amenable to total correction, requiring palliative procedures in the neonatal, infant and school age. These are pathologies of worse prognosis and that present greater morbidity and mortality between the stages of Correction, evolving to heart transplantation in adulthood. The atresias of the large arteries (pulmonary and aorta) and valves (mitral and tricuspid) are classified here, as they also occur with hypoplasia of the ventricles. See Figures 1 and 2 with the possible related ICDs.

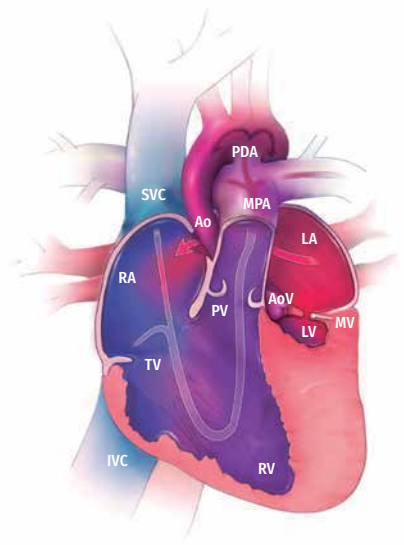
HYPOPLASIA OF THE VENTRICLES (RIGHT AND LEFT)

Figure 1 – Hypoplastic right heart syndrome (Q22.6)



Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).
Q22.4 Congenital stenosis of the tricuspid valve.

Figure 2 – Hypoplastic left heart syndrome (Q23.4)



RA. Rigth Atrium
RV. Right Ventricule
LA. Left Atrium
LV. Left Ventricle

MPA. Main Pulmunary Atery
Ao. Aorta
SVC. Superior Vena Cava
IVC. Inferior Vena Cava

TV. Tricuspid Valve
MV. Mitral Valve
AoV. Aortic Valve
PV. Pulmonary Valve

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).
Q23.0 Congenital stenosis of the aortic valve.
Q23.2 Congenital mitral stenosis.

The neonatal procedure usually indicated is the maintenance of patency of the ductus arteriosus through the placement of stent or performing a shunt with placement of a prosthesis and its variations of this as, for example, the shunt from Blalock-Taussig.

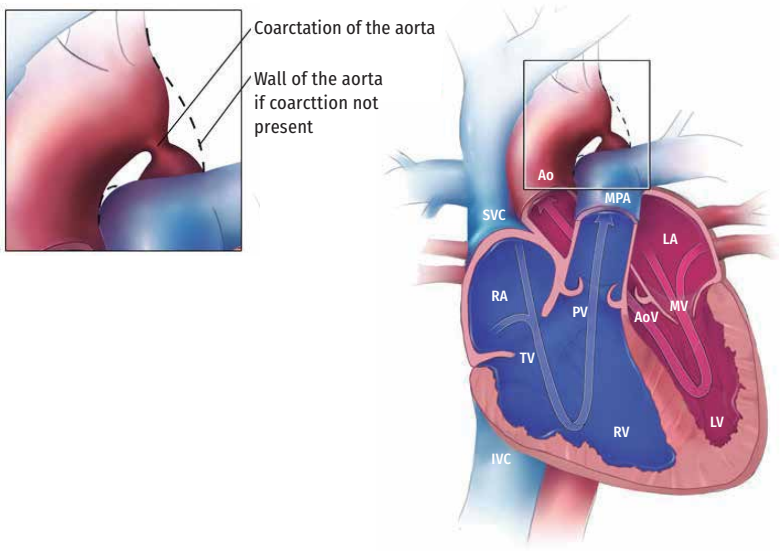
The procedure indicated in the infant period, usually up to 2 years (depending on the degree of cyanosis and heart failure that the patient develops), is cavopulmonary anastomosis or Glenn surgery and, finally, at school age, total cavopulmonary anastomosis or Fontan surgery is indicated.

Thus, the surgical planning for these children, throughout their lives, is already known and quite different from the others in which non-invasive procedures and total correction are possible.

STENOSES AND HYPOPLASIA OF THE LARGE ARTERIES (AORTA AND PULMONARY)

They are pathologies with a wide range of anatomical and clinical changes ranging from critical aortic coarctation with neonatal repercussion (which requires surgery as soon as possible) and critical pulmonary stenosis (which requires balloon dilation). Both are examples of critical heart diseases that have an optimal prognosis, low mortality, total correction and normal quality of life in the long term. Unlike the tetralogy of Fallot, which also occurs with pulmonary stenosis, and which may or may not require neonatal procedure of shunt or complete correction with good prognosis throughout the first year of life. Figures 3 and 4 represent the most common defects and their variants with related ICDs.

Figure 3 – Coarctation of the aorta (Q25.1)



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MV. Mitral Valve
AoV. Aortic Valve
PV. Pulmonary Valve

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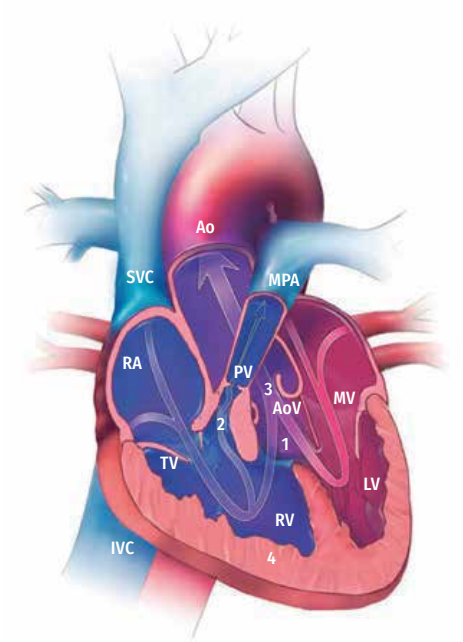
Ao. Aorta
SVC. Superior Vena Cava
IVC. Inferior Vena Cava

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).
Q25.2 Aortic atresia.
Q25.3 Aortic stenosis.

Figure 4 – Tetralogy of Fallot (Q21.3)



RA. Rigth Atrium
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MPA. Main Pulmunary Atery
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IVC. Inferior Vena Cava

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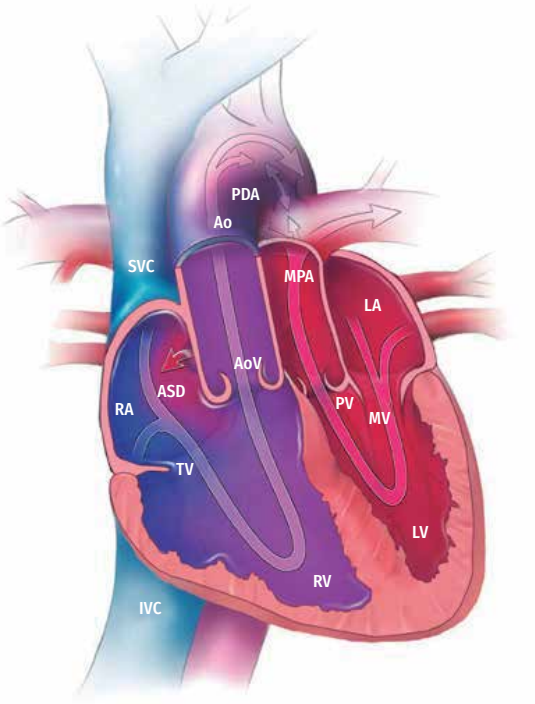
MV. Mitral Valve
AoV. Aortic Valve
PV. Pulmonary Valve

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).
Q22.0 Pulmonary valve atresia.
Q22.1 Congenital stenosis of the pulmonary valve.
Q25.5 Pulmonary artery atresia.
Q25.6 Pulmonary artery stenosis.

TRANSPOSITION OF LARGE ARTERIES OR LARGE VESSELS

Exchange of large vessels has complete correction in the neonatal period.

Figure 5 – Transposition of the great vessels



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Ao. Aorta
SVC. Superior Vena Cava
IVC. Inferior Vena Cava

TV. Tricuspid Valve
MV. Mitral Valve
AoV. Aortic Valve
PV. Pulmonary Valve

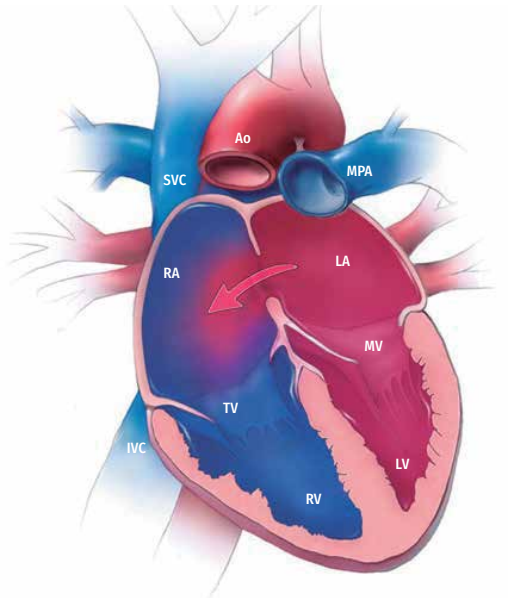
ASD. Atrial Septal Defect
PDA. Patent Ductus Arteriosis

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).
Q25.8 Other congenital malformations of the large arteries.
Q25.9 Unspecified congenital malformation of the large arteries.

COMMUNICATIONS BETWEEN CHAMBERS

It is the defects of the interatrial septum (Figure 6) and interventricular septum (Figure 7) or both (Figure 8) that depending on the size of the defect will give greater or lesser clinical repercussion. They are serious heart diseases with the possibility of total correction in the first year of life, after initial clinical treatment.

Figure 6 – Interatrial communication (Q21.1)



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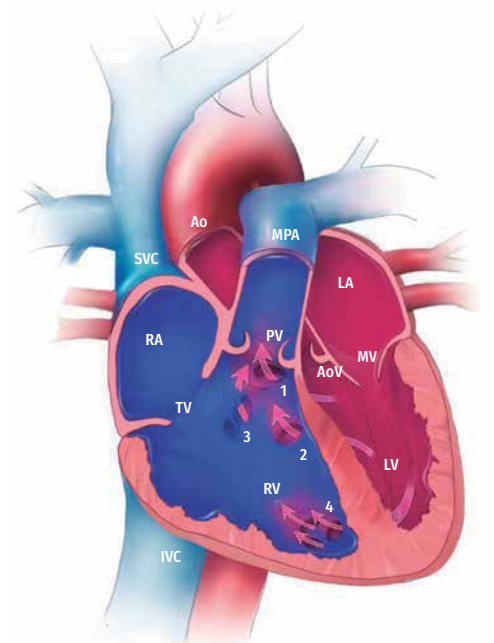
Ao. Aorta

SVC. Superior Vena Cava
IVC. Inferior Vena Cava
TV. Tricuspid Valve
MV. Mitral Valve

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).

Figure 7 – Interventricular communication (Q21.0)



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LV. Left Ventricle

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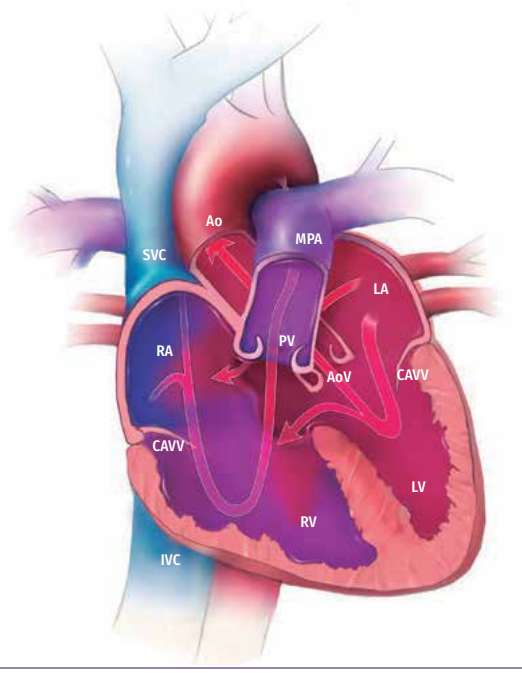
Ao. Aorta
SVC. Superior Vena Cava
IVC. Inferior Vena Cava

TV. Tricuspid Valve
MV. Mitral Valve
AoV. Aortic Valve
PV. Pulmonary Valve

1. Conoventricular, malaligned
2. Perimembranous
3. Inlet
4. Muscular

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).

Figure 8 – Atrioventricular communication (Q21.2)



RA. Rigth Atrium
RV. Right Ventricule
LA. Left Atrium
LV. Left Ventricle

MPA. Main Pulmunary Atery
Ao. Aorta
SVC. Superior Vena Cava
IVC. Inferior Vena Cava

CAVV. Common Atrioventricular Valve
PV. Pulmonary Valve
AoV. Aortic Valve

Source: Adapted from CDC (https://www.cdc.gov/ncbddd/heartdefects/facts.html).

PREVENTION

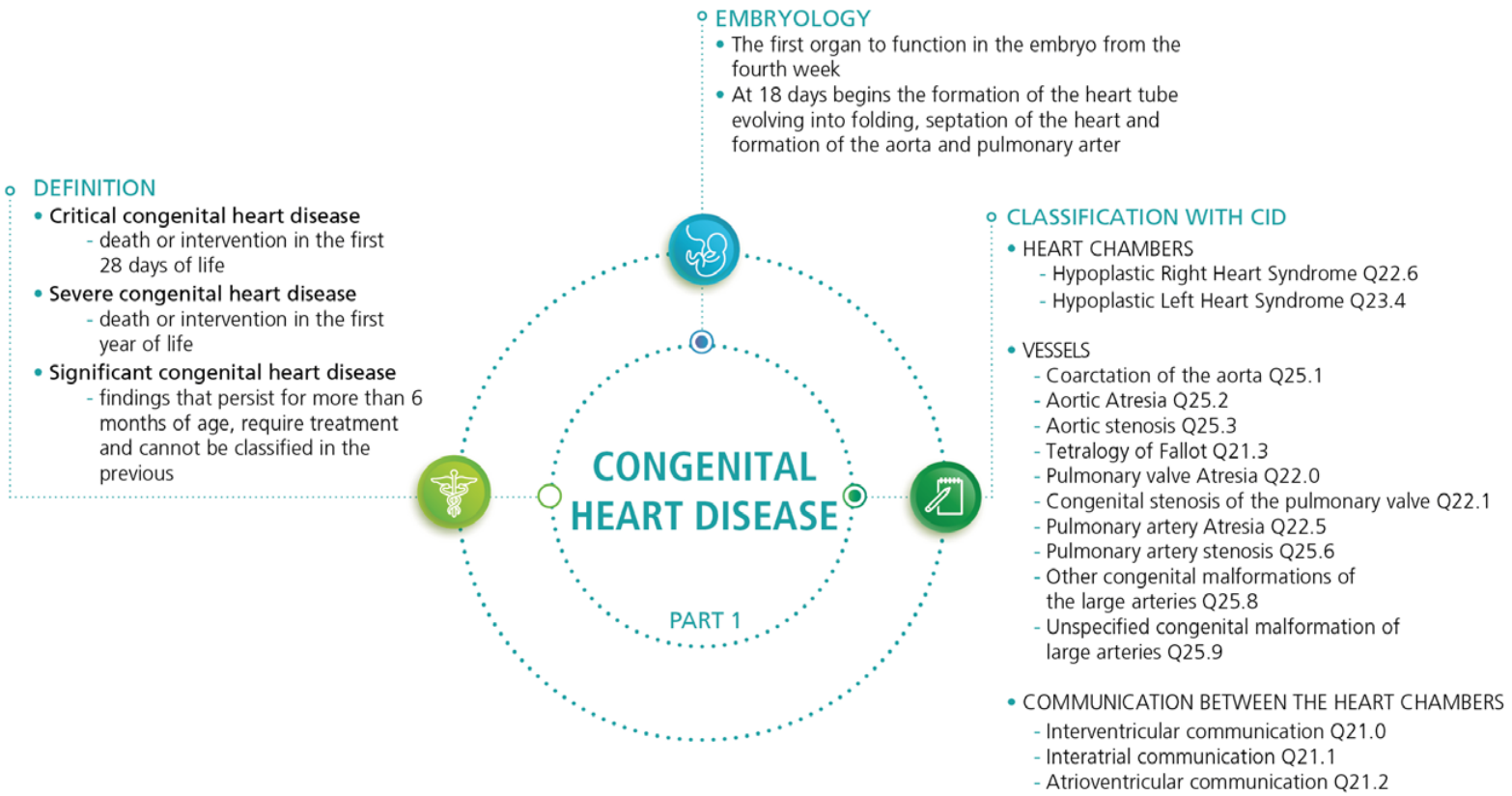
Given the high morbidity and mortality of CHD, its prevention should be thought out not only in the gestational period, but before, by preventing diabetes for women of childbearing age, as well as rubella vaccination and pregnancy planning. Therefore, prenatal monitoring is essential to monitor the clinical evolution of pregnancy and the risk factors related to the pregnant woman, enabling an assessment of the need for diagnostic complementation with additional examinations when suspected of CHD. Also become important measures, diabetes control disease and proper treatment of collagenoses, choosing the effective drug for the mother, but of lower risk for the conception whenever possible and observing the gestational period. The same is recommended for other maternal diseases such as epilepsy and heart disease.[14]

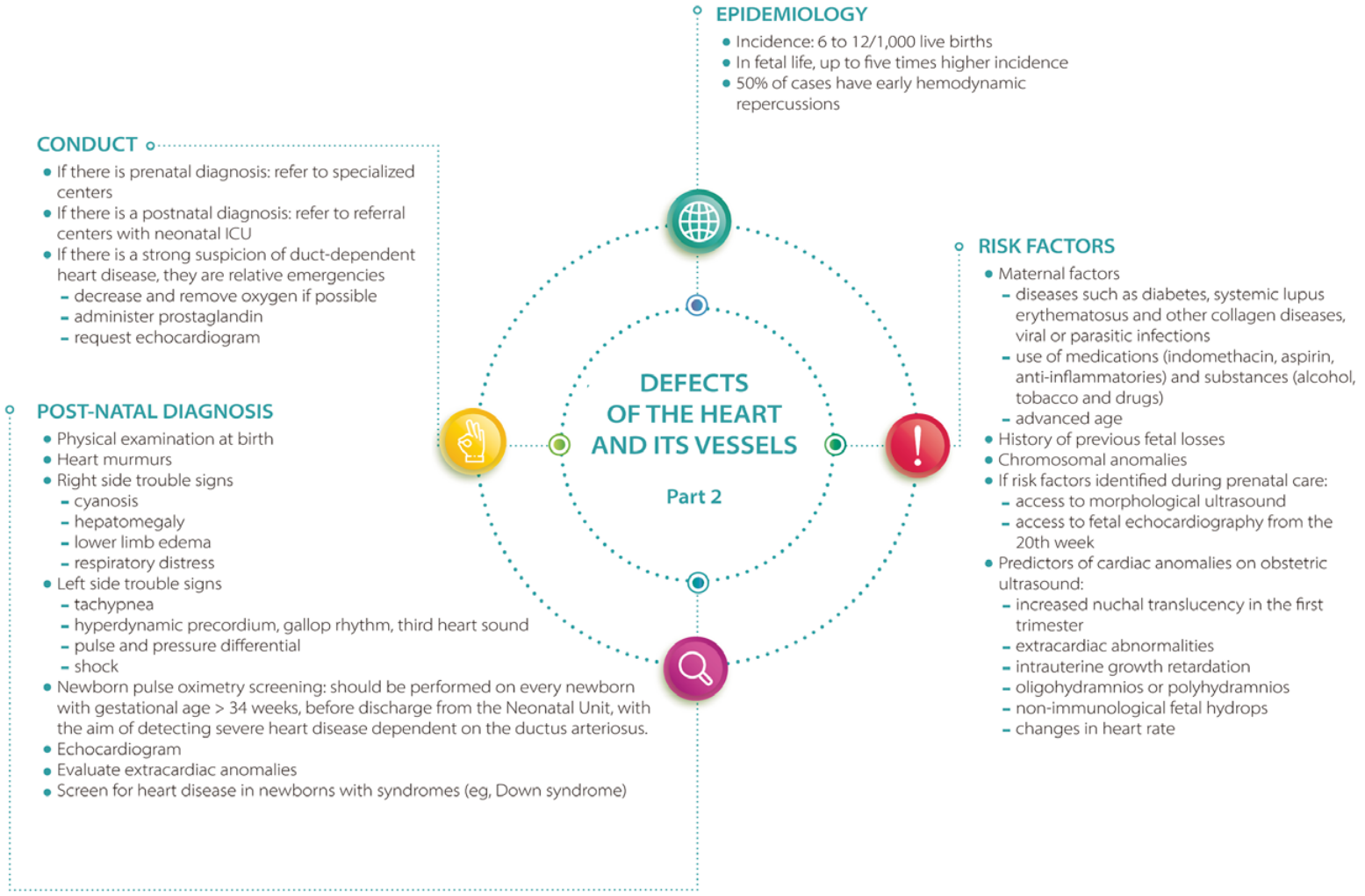
The prevention of CHD will have an impact on individuals and families and on the health system, since treatment often includes complex procedures, prolonged hospitalization and long follow-up. This book has a specific chapter that presents in more detail the prevention of congenital anomalies.

TO REMEMBER

- Cardiac abnormalities are defects that require specialized surgical procedures.
- Prenatal and neonatal diagnosis increases the chances of survival and decreases morbidity.
- Children diagnosed and properly treated may have normal life.

INFOGRAPHIC





Images source: WHO/CDC/ICBDSR, 2014.

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5 ORAL CLEFTS

SUMMARY

OBJECTIVE

To address topics about oral clefts and describe Embryology, classification, etiology, treatment and possibilities of clinical intervention, involving the different levels of health care.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

Oral clefts are the fourth category of congenital anomalies most prevalent in humans. These clefts occur due to defects in the formation of the primary and secondary palate at the beginning of embryo formation and are classified as cleft lip associated or not with cleft palate and isolated cleft palate. Clinically, oral clefts can occur as a single defect (isolated) or associated with other congenital anomalies (syndromic), with the involvement of genetic and non-genetic factors in their genesis. Oral clefts lead to eating and communication disorders, emotional and social problems. The prevalence and clinical consequences of these anomalies justify the recognition of the specific needs of the affected individuals and demand that specialized and multi-professional treatment be complementary to the routine care of primary care.

CONCLUSION

Oral clefts are frequent congenital anomalies that have a great impact on the health of the individual and their families. In this sense, these conditions are of great relevance in the field of Public Health and their notification should be prioritized.

KEYWORDS

Congenital abnormalities. Orofacial clefts. Cleft lip. Cleft palate.

DEFINITION

Oral clefts (OC) are craniofacial congenital abnormalities that affect the lips, oral and nasal cavities, known as cleft lip (CL), cleft palate (CP) and cleft lip associated with the cleft palate (CL/P). They correspond, as a group, to the fourth most common cause of congenital anomalies.[1]

EMBRYOLOGY

OC occurs due to incomplete formation of the lip and/or palate in the process of facial embryogenesis. The development of the face comprises one of the most complex events during embryogenesis, coordinated by transcription, growth and cell signaling factors as well as extracellular matrix proteins. Due to the complexity of events, this process is vulnerable to the action of environmental and/or teratogenic factors.[2]

The formation of the face occurs in two stages: development of the primary palate and development of the secondary palate.[3,4] Interference in any of the embryonic stages can determine OC. The formation of the primary palate determines the development of the upper lip and the anterior portion of the palate and occurs in the first weeks of gestation. The facial development is initially demarcated by the appearance of the prechordal plate at the cephalic end of the embryonic disc forming the stomata (precursor of the mouth and the anterior lobe of the pituitary) around the second week post conception. The primordial face is formed from the migration of ectodermal cells of the neural crest combined with mesodermal cells.[3] Around the fourth post conception week, thickening forms in the frontal eminence due to migration and mitotic proliferation of the ectomesenchyme. The first thickenings are the olfactory placodia that migrate anteriorly delimiting the nasal orifices establishing the frontonasal prominence (lateral and medial nasal processes). Nasal processes with the maxillary processes will form the middle portion of the nose, upper lip, anterior portion of the jaw and primary palate. The lower lip is formed by the two mandibular processes.[5,6]

The oral and nasal cavities should be separated at the 12th gestational week. The palate is an essential component for breathing, chewing, swallowing and speech. The secondary palate develops after the formation of the primary palate, being composed of the hard palate (anterior portion) and soft palate (posterior portion). Its formation (at the beginning of the sixth week of gestation), arises from the medial fusion of the Palatine crests, formed from the maxillary processes.[3] The Palatine crests or Palatine processes are initially directed downward, on each side of the tongue. The anterior portion of the hard palate forms as an extension of the premaxilla (medial Palatine process). With continuous growth, an apparent lowering of the tongue occurs, allowing the lateral palatine processes to advance towards the midline in the anteroposterior direction, forming the secondary palate. The movement and closure of palatine processes involve an intrinsic force whose nature has not been clearly determined. It is suggested that there is a relationship with the large number of proteoglycans and contractile fibroblasts in the region. Another factor involved with the closure of the secondary palate is the displacement of the tongue of the space between the Palatine crests due to the growth pattern of the head.[5,6]

EPIDEMIOLOGY

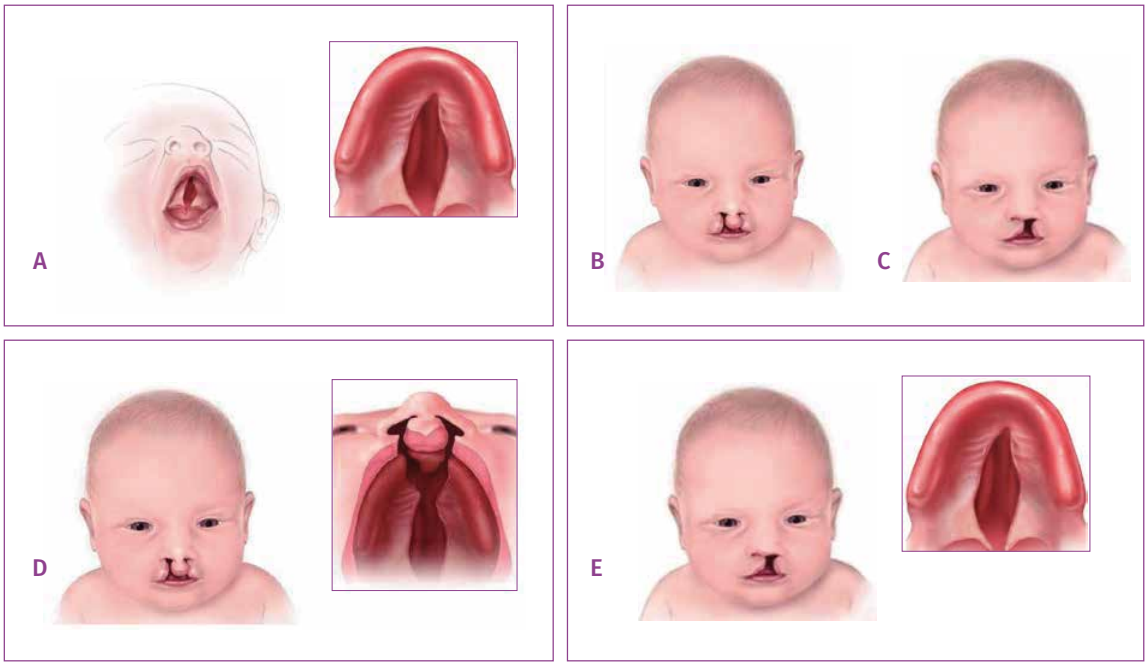
The overall incidence is approximately 1.5 per 1,000 live births, varying according to geographical region, ethnic origin and socio-economic level.[7,8] The prevalence in the Asian population is higher, being 2/1, 000 newborns, followed by the European population of 1/1, 000 newborns and less frequent in Afro-descendants of 0.41/1, 000 newborns.[1,8–11]

CLASSIFICATION

Anatomical Classification

Due to the development of the lip and palate involving different embryological structures and the period of development, FOS are classified into two groups: cleft lip associated or not to cleft palate and isolated cleft palate (Figure 1).[1,3,8,9]

Figure 1 – Scheme of oral cleft types: A) isolated cleft palate, B) bilateral cleft lip, C) left unilateral cleft lip, D) bilateral cleft lip and palate, E) left unilateral lip and palate cleft[12]



Source: WHO; CDC; ICBDSR. **Birth defects surveillance**: atlas of selected congenital anomalies. Geneva: WHO, 2014.

They can be characterized as:

- Cleft lip (CL): characterized by the failure of the fusion of the medial and maxillary frontonasal processes, that is, the primary palate. The CL has variable extension and can be complete when it reaches the lip, the alveolus and the nasal floor or incomplete when it does not affect the full extension of the lip or does not extend through the nasal floor, in addition the CL can be unilateral or bilateral.

- Cleft palate (CP): triggered by failure to fuse the palatine processes resulting in a cleft of the hard and/or soft palate.
- Cleft lip and palate (CLP): failure to fuse both the primary and secondary palate.

OC vary according to type, with CLP occurring in 1 every 600-800 births and CP in 1 every 2,000 live births.[7,8] Forty-five percent of the cases are CLP, 30% CP and 25% CL without association with cleft palate. In addition, OC frequencies also differ in gender and laterality. CL is more common in males, while CP is more common in females both in a ratio of 2:1. As for laterality, the left unilateral cleft lip is more common than the right unilateral cleft lip and the bilateral cleft lip in a ratio of 6:3:1.[2,8]

Clinical Classification

OC can be classified as non-syndromic OC, when they correspond to the only congenital defect present in the individual and syndromic OC, when they are associated with other congenital defects. These can be evident at birth or quite subtle, which is why clinical follow-up and follow-up of neuropsychomotor development are fundamental for correct clinical characterization.[13,14] For each of the groups, different etiologies are recognized.

ETIOLOGY

The etiology of OC is complex and involves genetic factors with variable interaction of environmental factors. About 70% of CL/P and 50% of IPF are non-syndromic, that is, they are not associated with other birth defects or developmental delay.

In this group, the etiology is complex and multifactorial with genetic and environmental aspects involved in its formation. In embryogenesis, before the completion of the primary palate, the nasal process has a peak of cell division, in this way it becomes susceptible to the action of some environmental components, among them are the consumption of alcoholic beverages, exposure to smoking (actively or passively), exposure to phenytoin, valproic acid, Thalidomide, as well as exposure to pesticides and herbicides such as dioxin.[1,4] The use of alcohol during pregnancy in addition to compromising fetal development, increases the risk for lip and palate cleft by 1.5-4.7 times being dose dependent.[15] A study using an animal model showed that exposure to alcohol during pregnancy can affect gene expression via epigenetic modifications (DNA methylation) mainly in alcoholic fetal syndrome.[16]

As for smoking, it is known that cigarettes contain a large number of chemical toxins, being a risk factor for OC. In a meta-analysis performed to verify the effect of maternal tobacco use on oral clefts, the relative risk for O/PC was 1.34 (95%CI: 1.25-1.34) and for IPF of 1.22 (95%CI: 1.10-1.35).[17] Various studies demonstrate a relative risk of 1.3-1.5 and when maternal smoking is associated with genetic factors this risk is more significant, and can increase by 7.16 times.[3] Genes related to detoxification of cigarette components such as N-acetyl transferase (*NAT1* and *NAT2*), Cytochrome P450 (*CYP1A1*) and S-transferase (*GST*) demonstrated a dose-response effect on tobacco use in the first trimester of pregnancy.[18-20]

Association studies have identified variants in several genes associated with OC, among them are the *IRF6, TGFA, MSX1, SPRY1, MSX2, PRSS35, TFAP2A, SHH, VAX1, TBX10, WNT11, PAX9, BMP4* among others.[3,4,21–23]

Syndromic forms of OC occur secondarily to monogenic diseases, chromosomal abnormalities, teratogenic factors and Uncategorized syndromes.[2,3,24,25]

TREATMENT AND PREVENTION

CL can be diagnosed in the prenatal period through ultrasound imaging examination. CP are, in general, diagnosed at birth, by clinical examination.

The so-called tongue test was regulated as a strategy for diagnosing of still in the maternity environment shortly after birth, enabling rapid referral to referral services when necessary and guidance to parents about care. However, a study conducted in Brazil observed that 44% of cases of CP are diagnosed after discharge from maternity.[26]

OCs require early diagnosis and multi-professional care, as they cause oral, eating and Communication Disorders, otological complications leading to hearing loss as well as emotional and social problems.

Babies born with OC have eating disorders such as insufficient sucking, regurgitation of milk in the nasal cavity, and low-calorie gain.[27] These factors can hinder weight gain and can delay surgical planning.[28] The guidance on feeding at birth is fundamental and many children manage to stay with exclusive breastfeeding. Despite the recommendations in Brazil on breastfeeding, the nasogastric tube (SNG) was used as the first power source in 21% of cases.[29] Newborns with OC are able to feed orally in the first hours of life and the use of SNG is often unnecessary.[30] Health professionals should give preference to breast-feeding or non-invasive methods. For this – and in view of the prevalence of OC – the recognition of the intrinsic needs and possibilities of non-invasive dietary intervention for this group of individuals should be part of the proposals for continuing education of health professionals working in maternity hospitals and Primary Care.[29]

In Brazil, the treatment of OC is guaranteed by the Unified Health System through the Reference Network in the treatment of craniofacial deformities. These referral services mainly rely on surgical staff, speech therapists and dentists. Services are distributed in all regions of Brazil, however, there is a regional inequity, as most are concentrated in the Southeast Region.[30] Newborns should be referred as soon as identified to the reference services for multi-professional care.

Genetic evaluation is essential because it will allow a correct etiological diagnosis and genetic counseling. In cases of syndromic OC, the risk of recurrence will be according to the etiology (chromosomal, gene or teratogenic). In non-syndromic OCs of multifactorial etiology, the risk of recurrence will depend on the type of cleft, family history and identification of risk factors capable of prevention. For this group, it is recommended to use periconceptional folic acid to prevent the recurrence of OC.[31] However, access to genetic evaluation is limited.[32]

BRAZIL SKULL-FACE PROJECT

Brazil skull-face Project (PCFB) is an initiative of a group of researchers whose main objective is to bring subsidies to improve health care for individuals with craniofacial anomalies. It is an interinstitutional, multicentric, multi-professional and voluntary initiative that has been active since 2002.

Currently, the PCFB involves ten different genetic or specialized care services in OC.[32] This proposal covers four different lines of action:

- **A** Aspects of public health and craniofacial genetics.
- **B** Multicenter studies in OC and 22q11.2 deletion syndrome (most common cause of syndromic OC).
- **C** Education strategies focused on the population and health professionals.
- **D** Brazilian Base of Craniofacial Anomalies (BBAC).

The strategies proposed by the PCFB are examples of the incorporation of research in health care. Among them, the BBAC allows the recognition of specific population characteristics, individuals with similar genetic research needs, optimizing scarce laboratory resources, and the identification of regional risk factors, which can support proposals for the education of the population and health professionals.[33] The PCFB developed a training course for presurgical feeding of babies with OC, aimed at students of health professions and professionals of Primary Care and maternity.[32]

The Union of these initiatives of the PCFB resulted in a line of research linked to the Public Policy Program for SUS (PPSUS) in Alagoas, which does not have a high-complexity service for the treatment of OC. Involving the agreement between the State Health Department, Municipal Managers and maternity hospitals of the state, a system of reference and counter-reference of babies with OC for genetic evaluation was created in the only public service of the state. To this end, instructional material was developed and training of professionals for care in primary care and maternity hospitals was carried out. This proposal remains active and has subsidized the construction of public policies for the state of Alagoas.[33] Similar design could be implemented in other Brazilian states.

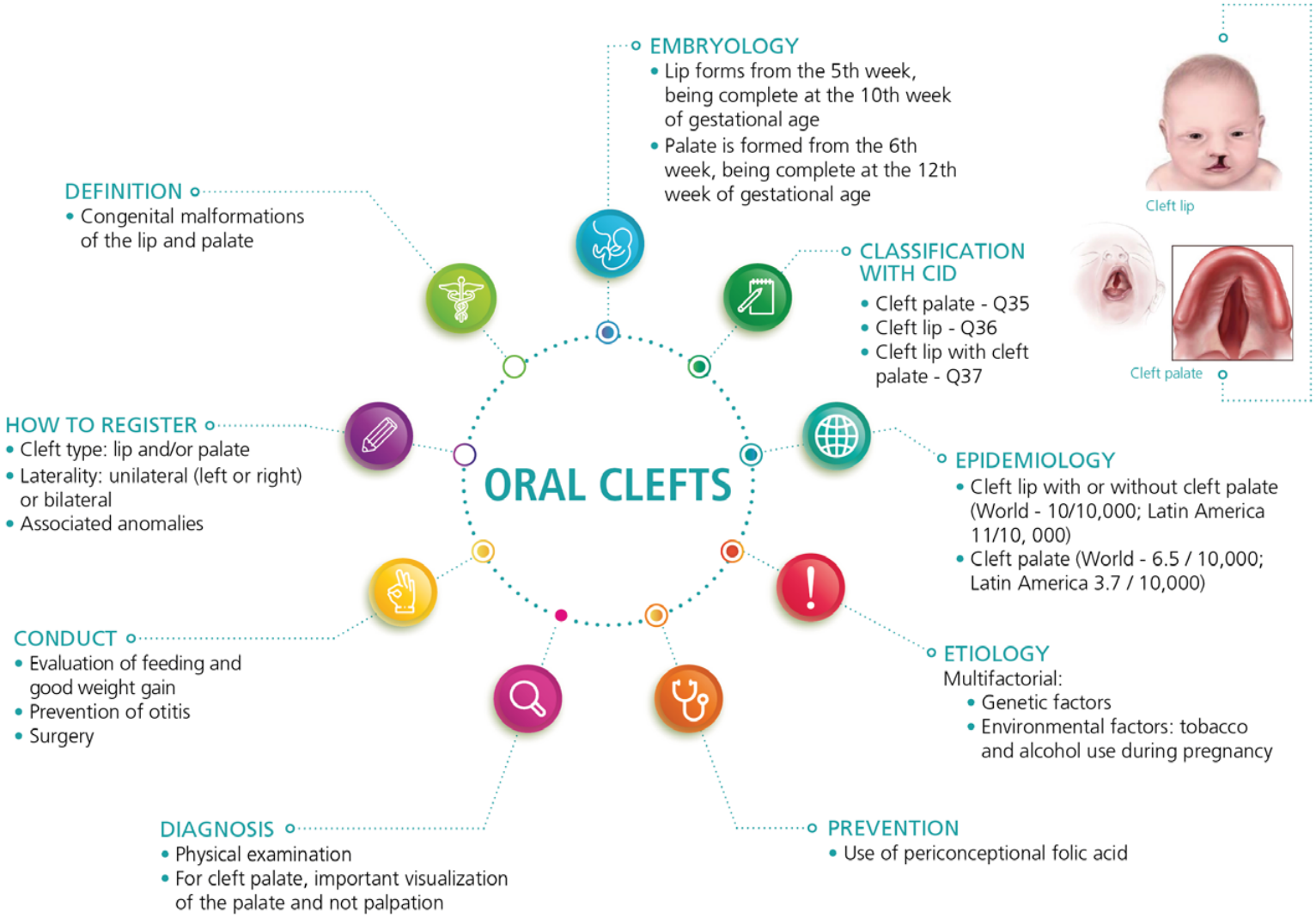
CONCLUSION

OCs are frequent birth defects that require prolonged rehabilitative treatment and that should involve different professionals and levels of health care. The etiological clinical diagnosis, for which genetic evaluation is essential, is not yet available on a large scale in our country and it impacts the genetic counseling of families, as well as the epidemiological recognition of syndromic and nonsyndromic OC in the Brazilian population. Population impact strategies, such as those developed by the PCFB could favor general and larger-scale health care in our country.

TO REMEMBER

- Oral clefts are frequent congenital anomalies that cause great impact on the health of individuals and their families.
- They are classified as cleft lip associated or not to cleft palate, or isolated cleft palate, and may be syndromic (when another congenital anomaly is present), or non-syndromic (isolated).
- They are mainly caused by genetic factors associated with such as smoking and consuming alcohol during gestation.
- Early diagnosis and adequate management, especially breastfeeding, are required, as well as referral to referral services with a multi-professional team.
- Genetic evaluation is necessary for etiological diagnosis and genetic counseling.

INFOGRAPHIC



Images source: WHO/CDC/ICBDSR, 2014.

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GLOSSARY

Syndrome: pattern of congenital anomalies determined by a common cause.

Genetic counseling: communication process of diagnostic, etiological, therapeutic aspects and risk of recurrence of genetic conditions.

22q11.2 deletion syndrome: a syndrome caused by deletion of the 22q11.2 chromosomal region leading to cleft palate, heart disease, typical face, immunodeficiency and developmental delay.

6 GENITAL ABNORMALITIES AND DISORDERS IN SEXUAL DIFFERENTIATION

SUMMARY

OBJECTIVE

To address topics on disorders of sexual differentiation (DSDs) and hypospadias, describing their definitions, their risk factors and their epidemiology.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

Atypical/undifferentiated genitalia are part of a large group of genital abnormalities in which phenotypic sex cannot be clinically defined. Research for the best sexual designation depends on genetic research, in which the karyotype is the initial and not definitive reference of the research, and hormonal evaluation, evaluating gonadal and adrenal axes, covering etiology and prognosis for puberty and fertility. Surgical management after diagnosis ponders family decision, evaluation of the patient's body and emotional development and fertile potential, evaluating the best time for an intervention. In addition, parents should have psychological support during the process, have doubts and expectations clarified and supported by the care team during the definition of treatment.

CONCLUSION

Disorders of sexual differentiation should be adequately identified, registered and monitored in tertiary hospital by a multidisciplinary team from birth until after treatment.

KEYWORDS

Congenital abnormalities. Hypospadias. Indeterminate sex. Disorders of sexual differentiation Information systems. Surveillance in public health.

INTRODUCTION

Defects of the external genitalia are classified as major malformations (structural change in an organ, or part of the body that requires a surgical therapeutic solution) and presume changes of the internal genitalia. Observation of such defects does not go unnoticed in most cases, which makes it possible to conduct a correct registration of this congenital anomaly (CA). Given the phenotypic variability of external genital defects and the complexity of their etiology, we will briefly describe the most common causes, clinical and therapeutic consequences, as well as the importance of care by a multi-professional team of these children and their families. The proper description of the observed anomaly will be described in topics.

Most of the genital defects addressed in this review include, in their etiology, those resulting from disorders of sexual differentiation (DSDS). Hypospadias will also be discussed in this review due to their high incidence and proximity to DSD. Anomalies defined as malformational sequences: bladder exstrophy with epispadias, cloaca persistence and urorectal septal defects, will not be included in this text.

An atypical or indeterminate genitalia is occurs when phenotypic sex of newborns, infants, adolescents and even adults cannot be defined clinically. The use of the term "ambiguous genitalia" tends to be abandoned because of its negative psychological impact on these families. DSDs include several diseases that occur by various pathophysiological mechanisms, however atypical genital presentation of newborns is presented as a finding in most of these patients. These conditions present failure of the genetic information, based on genes and chromosomes, of gonadal differentiation, culminating in the phenotypic expression of the structures.[1]

These disorders have already been described in the past as hermaphroditism and then as intersex.[2,3] However, in 2006, with the publication of the Chicago consensus, it was decided to change this denomination to something less stigmatizing and with a broader concept, so the term DSD appeared.[3] In addition, with this new nomenclature, the etiological tables were divided into large groups (Chart 1), according to the karyotype, thus being designated: DSD 46, XX; DSD 46, XY and ovotesticular DSD, DSD 46, XX testicular, DSD 46, XY complete gonadal dysgenesis.[3]

Chart 1 – Exchange in the use of the terms of intersex disorders by DSD, adapted from *Consensus Statement on Management of Intersex Disorders*[3]

NUEVO TÉRMINO	TÉRMINO ANTIGUO
46, XY DSD	Male pseudo-hermaphroditism; patient XY not virilized, not masculinization of patient XY
46, XX DSD	Female pseudo-hermaphroditism, patient XX supervirilized, patient masculinization XX
Ovotesticular DSD	True hermaphroditism
46, XX testicular DSD	Man XX or XX reverse sex
46, XY complete gonadal dysgenesis	XY reverse sex

Source: Adapted from Lee *et al.*
Note: DDS – Disorders of sexual development.

In 2016, a revision of the consensus was published, ratifying the nomenclature established in 2006.[4] This document also reinforced the importance and need for the research and management of DSD frameworks to be carried out by an experienced multi-professional team in a large regional center, since it can concatenate better resources (both human and technological) for management and, when necessary, for propor investigation.[3-5]

The team consists preferably of medical geneticist, endocrinologist, pediatrician/neonatologist, pediatric surgeon/urologist, gynecologist, radiologist, pathologist, psychologist or psychiatrist, social worker, nurse and bioethical professional. This team can be arranged in a multidisciplinary, interdisciplinary or transdisciplinary way. In addition, parents/guardians have a fundamental role in decision-making, so their instrumentalization by the multidisciplinary team is very important.[4]

Because they group rare and complex diseases, they require care in a tertiary hospital where there is an experienced multidisciplinary team. This care will be given not only during the diagnostic investigation and treatment, but during the longitudinal follow-up of these patients.[3,4,6]

At birth, the occurrence of a genital anomaly is up to 1:300 live births, but if we consider a malformation that is considered a genital undifferentiation, the prevalence changes to 1:4,500 live births.[1]

Hypospadias is an abnormal opening of the urethra (urethral meatus) in the ventral face of the penis, with or without ventral shortening (called Chordee). This may appear as an isolated anomaly, or in association with cryptorchidism and Müllerian remains, in Robinow, Smith-Lemi Opitz and WAGR syndromes.[7]

Hypospadias are one of the most common male forms of genital abnormalities. The lightest forms are distal, below the end of the glans. The most severe cases, called proximal, are located near the perineum.[8] Although it does not have a known cause, some risk factors can be identified, such as: genetic, hormonal, enzymatic, androgenic and environmental. There is a described family incidence of up to 25%. And it is currently discussed whether the increased incidence of this anomaly, in Europe and in the US, it would have as supporting factors an association with maternal age, vegetarian diet of the pregnant woman and housing in large urban centers.[7-9]

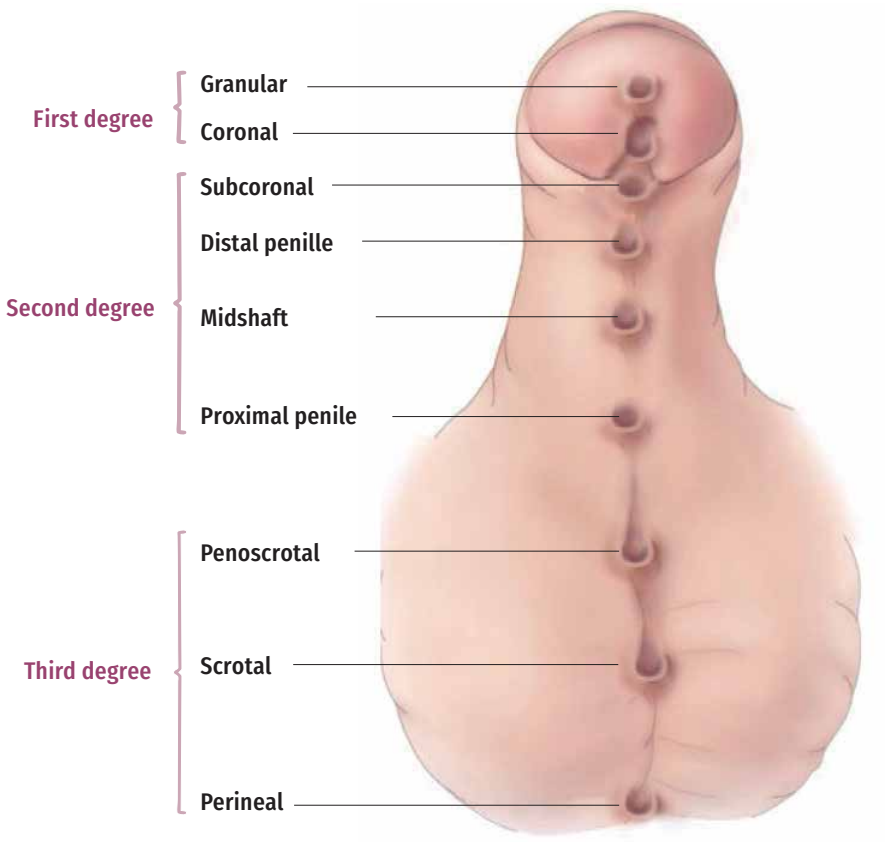
In a study published in 2019, from São Paulo/Brazil, the incidence of hypospadias was 0.7/1,000 live births. The locations of the urethral meatus in this study were 64.5% distal, 13.4% mean and 22.1% proximal.[10] The incidence of hypospadias on different continents in 2012 was 7.14/10,000 LB in Latin America, 24.47/10,000 LB in Canada - Alberta and 35.27/10,000 LB in Italy/Lombardy.[11]

PHYSICAL EXAMINATION

In cases of hypospadias, locate the urethral meatus and, if possible, observe an episode of diuresis. The complete nomenclature of hypospadias depends on where the location of the urethral meatus (Figure 1). The closer to the scrotum the opening of the urethra is, the more is the difficulty that patients may have to direct the jet of urine. By means of palpation, locate

the testicles in the scrotal or inguinal region. When it is not possible to locate the testicles by palpation, a transilluminator can be used in the scrotum. Observe if there is curvature of the penis, with excess skin in the dorsal part and scarcity of skin in the ventral part. When there is ventral shortening with consequent ventral curvature of the penis, this is called *Chordee*.[7]

Figure 1 – Nomenclature of hypospadias according to the location of the opening of the urethra



Source: Adapted from CDC (https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/photo-atlas/gen.html).

There is an important association between hypospadias and DSD. In studies that evaluated the differential diagnosis of genital abnormalities, patients in which cryptorchidism and hypospadias coexisted, the incidence of DSD reached 27%. If the gonad is not palpable at clinical examination, the risk of an intersex condition increases by three times. Similarly, the more posterior the position of the meatus (the higher degree of hypospadias), the higher the probability of DSD.[12]

In the physical examination of hypospadias it is necessary to measure the length of the penis, from the pubis to the top of the glans, which should be proportional to the expected gestational age at birth. If the patient has a different measure than expected for gestational age, that is, up to 2.5 standard deviations, we cannot rule out the possibility of a DSD. For full-term newborns, this minimum measure is 2.5 cm. This and the other expected measures are described in Table 1.[12]

Table 1 – Penis size (in centimeters) for different ages

AGE	MEAN ± STANDARD DEVIATION	AVERAGE – 2.5 STANDARD DEVIATIONS
RN – 30 weeks	2,5 ± 0,4	1,5
34 weeks	3,0 ± 0,4	2,0
Term RN	3,5 ± 0,4	2,5
0-5 months	3,9 ± 0,8	1,9

Source: Adapted from Damiani.[12]

Anatomical types that do not fit into the previous descriptions should be urgently evaluated by a geneticist, surgeon, endocrinologist and psychologist for suspicion of DSD. The prompt identification, as well as an adequate description, of an undifferentiated genitalia is the indispensable starting point for adequate management of a DSD case. As defined by the 2006 consensus, the following tables are classified as undifferentiated genitalia:[3,4]

- Obvious genital undifferentiation.
- Apparently female genitalia with increased clitoris, posterior labial Fusion or mass in the inguinal/labial region.
- Apparently male genitalia with bilateral cryptorchidism, isolated perineal hypospadias or mild hypospadias with cryptorchidism.

In the description of the physical examination of a newly diagnosed undifferentiated genitalia, it is extremely necessary to avoid the use of nomenclature that may induce a sex designation. For this, the names referring to embryological structures are used, being as follows: phallus (for the corresponding to the clitoris or penis), whose measurement in centimeters must be described together; labioscrotal protrusions (for the corresponding to the labia majora or the scrotal bag), whose degree of fusion must be described (absent, partial, total), as well as their appearance (roughness) and pigmentation. In addition, it is important to describe the position of the urethral meatus (perineal, scrotal, penoscrotal, at the tip of the phallus), as well as whether or not there are palpable gonads (and their location: absent, inguinal, labioscrotal).[3]

It is important to note that there are also scales that facilitate the description of an undifferentiated genitalia.[13]

GENETIC RESEARCH

The advance in the knowledge of molecular mechanisms in relation to the delicate balance sexual determination/differentiation has established a new level, in which only the presence of the sex chromosomes XX and XY is not a definitive attribute in the designation of sex to the newborn, although the use of the karyotype is still the initial reference to begin the investigation of a baby with indeterminate genitals. Being the peripheral blood karyotype, GTG Bands pattern, the choice.[1,14]

There are a number of molecular biology tools available that assist in this investigation. The request for the extraction of DNA (deoxyribonucleic acid) for the investigation of some genes is a reality present in reference centers in Brazil.[15]

The search for *SRY, SOX9, WNT1* and other genes can be obtained in analysis panels that cover most of the changes responsible for DSD. The use of *FISH* (Hybridization *in situ* fluorescence) is limited, since it requires a specific diagnostic hypothesis, for example, to look for X or Y lines in the suspected mosaicism. The method called MLPA (link-dependent multiple probe amplification) is a method hardly used in routine, but that can be used in specific panels for DSD genes: *NR0B1, SOX9* and NR5A1.[15]

Chromosomal analysis by microarrays (*array-CGH; GH*) is useful as long as properly requested and interpreted. We suggest the request by a geneticist doctor. They serve to evaluate microdeletions and microduplications whose sizes are not detected in a GTG karyotype, has the drawback of not detecting balanced rearrangements.[15]

PCR (polymerase chain reaction) is already part of many routines, in several specialties. In the diagnostic evaluation for DDS, it serves to identify the presence of SRY, even in DSD 46, XX, search for “cryptic " Y in DDS 45, X/46, XX.[15]

New generation sequencing (NGS), sequencing, panels (genes for DSD), exome or genome sequencing are excellent tools if well requested and well interpreted.[14,15]

HORMONAL RESEARCH

Hormonal evaluation is one of the bases of etiological research, as well as provides important information regarding the prognosis for spontaneous puberty and fertility. The choice of which endocrinological axis will be primarily evaluated (gonadal axis or adrenal axis) is guided by the presence or not of palpable gonads at physical examination. In the case of an undifferentiated genitalia without palpable gonads, the priority is to investigate the adrenal axis to rule out a picture of congenital adrenal hyperplasia (HAC), especially the classic forms of 21-hydroxylase deficiency.[4] This is the most prevalent form of DSD in individuals with karyotype 46, XX and its classic salt-losing form is a life-threatening condition.[5]

Therefore, it should be carried out, from the 3rd day of life, dosages especially of 17-OH-progesterone, androstenedione, electrolytes (sodium and potassium), ACTH and renin.[5] This adrenal evaluation can be expanded if there was suspicion of rarer forms of HAC such as: deficiency of 11-β-hydroxylase, 3-β-hydroxysteroid - dehydrogenase types II, 17-α-hydroxylase/17,20-lyase (the latter is the second most prevalent form of HAC in Brazil). Remembering that some of these rare forms can manifest as undifferentiated genitalia both in individuals 46, XX and 46, XY.[5]

On the other hand, when there is palpable gonad, this speaks more in favor of DSD 46, XY or DSD with alteration in sex chromosomes. Thus, the evaluation of the gonadal axis should be initiated, with dosages mainly of FSH, LH, total testosterone, dihydrotestosterone (DHT) and androstenedione. However, these dosages require a particularity so that their result is reliable,

they must be collected in the period of mini-puberty. This period, the peak of which is between the 30th and 90th day of life, is a time when the gonadotropin axis is physiologically activated.[16,17] Mini-puberty is a window of opportunity not only for an adequate laboratory evaluation but also prognostic for puberty itself. After this period, the gonadotropin axis becomes quiescent and the evaluation of the production of gonadal sex steroids (especially testosterone and DHT) is only possible after a stimulus test with recombinant HCG or indirectly, by dosing other gonadal hormones, the production of which is active in childhood, such as anti-Müllerian hormone (AMH) and/or inhibin B.[5,16] These are good markers of gonadal function, but their testeting are not available in all centers in Latin America.

In addition, it is important to note that both DSD 46, XY and chromosomal DSD may present without palpable gonads, as well as rare forms of HAC (but not 21-hydroxylase deficiency) may present palpable gonads. However, they are fewer common presentations and we must hierarchize the hormonal assessment as described earlier to later, depending on the case, look for the rarest forms.

All patients with hypospadias, even isolated, should perform urination urethrocystography and ultrasound of the urinary tract. Vesicoureteral reflux may be present in around 10% of cases, which increases the risk of urinary tract infection and its consequences.[7]

SURGERY

Regarding the surgical management of these patients some important aspects should be highlighted, parents/guardians be aware of the risks and benefits of the procedures indicated for genital adequacy. The option of postponing surgery should be offered to the family, there are professionals who defend this approach currently. However, most scientific evidence still points to genital correction in the first year of life as the best option.[6,18] Most experts consider that complications occur in smaller numbers at this stage. In addition, emotional, cognitive and body image development can be affected if surgery is delayed. It is emphasized that irreversible surgeries should be avoided in this period. A fertility potential should be considered for decision making. There are several techniques to be employed, which can be chosen according to each case.[6,18]

When opted for feminizing genitoplasty, combined procedures are indicated; then adapting the external aspect, as well as separating the urogenital sinus when present. Thus, clitoroplasty, vaginoplasty, urethroplasty and vulvoplasty are performed at the same time.[6,18] When the patient does not have a urogenital breast and will need a neovagina, it is chosen to perform the correction of the external genitalia (clitoroplasty and vulvoplasty), leaving the construction of the vagina for after puberty.[6,18]

In patients whose breeding sex is male, the objectives of the correction are a straight penis, with the urethral meatus closer to the tip of the glans, with appropriate penopubic and penoscrotal angles and the fixation of the testicles when indicated.[6,18]

Regarding the management of the gonads there was no major change. In the presence of y material in the karyotype, gonadectomy is very important in cases of dysgenetic gonads or ribbons. In patients with complete androgen insensitivity, the current recommendation is gonadal

preservation for induction of puberty spontaneously. It is very important to maintain close follow-up of these patients. In patients with ovotesticular DSD, when possible, partial gonadectomy can be performed, preserving the portion in congruence with the sex of creation.[4,6] And, for patients with isolated hypospadias, the conduct is surgical correction, between 6 and 12 months of life.[6,18]

PSYCHOLOGICAL ASPECTS

Like any type of malformation, the diagnosis of DSD can cause considerable distress in the patient's family, especially in the period of etiological investigation. Diverse feelings can be experienced by the couple/family, emerging, in this context, social and cultural issues that can further hinder the elaboration of conflicts linked to this condition.[19]

It is evident that in the absence of complete information to patients and their families, these individuals demonstrate greater difficulty in dealing with the processes of diagnosis and its treatment.[4] Providing clear information to parents from the start is critical. When the baby is born in a health center whose team is not sufficiently prepared to start the etiological investigation, it must be continent with the parents, welcoming them and putting them in touch with the situation of uncertainty about the sex of the baby and avoiding information that is not based on established and updated evidence on DSD. This team should have the responsibility not to give false expectations and not to suggest that the child “seems” to be male or female, or even that it has two sexes. In these situations, the ideal is that they have a frank conversation with family members and say that they do not yet have precise answers on the etiology of DSD, but that this investigation will be carried out in a reference center that will have what to offer in terms of definition and treatment. If there is no psychologist in this center, the very team that is involved with childbirth and first care must provide ongoing support to parents, reassuring them and helping them to cope with the uncertainty of the moment and the need for the time that the investigation requires.[19,20]

During the period in which the baby is being investigated and which remains without a definition of sexual identity and without civil registration, the parents present important suffering. They are confused in the face of pressure from the extended family and friends about the sex of the child, not knowing how to break the news. In these cases, both the option of hiding the facts and lying, and the option of sharing the truth are seen as negative. When they hide the facts, in the long run, it can give the child a conception that their condition is something they have to be ashamed of. Spreading this to other family members and close friends, on the other hand, can promote the stigma of the child. The social environment, also depending on the current culture, often have difficulties in tolerating "rare" conditions. The lack of knowledge about the phenomenon of DSDs, in turn, causes in the lay public prejudiced reactions against the child and the family.[20]

When psychological monitoring of parents is being parallel to the etiological investigation of DSD, it is the role of the psychologist to evaluate their previous expectations, not only in relation to sex, but what degree of idealization exists in the couple's imagination. It should also check if there is a previous psychopathological picture of any of the parents, and psychic disorganization may occur in the face of this adverse event. It is the task of this professional to stimulate parents'

access to evidence-based information, seeking that they appropriate the clinical condition of their baby, the tests that need to be performed and what each of these tests brings information to the establishment of the diagnosis.[21]

Parents' doubts and fantasies are normal, especially in the initial period. It highlights the relationship between the disease and the sexual orientation of their children in adulthood, or even whether a future gender identity congruent with the designated sex will be possible. Parents may suffer a shock with the diagnosis and with the questioning of the sex of the baby, associated in large part with uncertainties of the development of the children and this, in a way, includes the psychosexual development of their children. Such concerns are related to the social experience of the parents themselves and the need for classification of children within the male-female gender categories.[18]

Another relevant yearning is related to the fertility of children in the future. The potential for fertility in cultures or communities awaiting procreation was discussed in this study. In these cases, infertile individuals are less valued as spouses, which generates anxiety in parents in certain cultures.[22]

The fact that this investigation is carried out by the multidisciplinary team that works with cases is a subject to be treated in psychological care, because parents will have to live with different doctors, of many specialties, during an interval of about 20 days, which is the average time in which the investigation unfolds. For parents, it is important that they have with the team a reference doctor, who will be in charge of centralizing the correct information that can be shared with them while the etiological investigation process takes place. The psychologist is expected to establish a communication link between parents-family-team, mediating anxieties and expectations, helping to clarify the clinical situation arising from doctors.[23]

At this first moment, in the etiological investigation phase, parents deal with the fear of the unknown, with the mourning for the baby that had been previously idealized and that was not constituted and with the guilt coming from having generated a child with malformation. Psychological intervention is necessary to address these issues and help parents prepare for the sexual designation that the child should receive, with the treatment plan and, consequently, with the sex of upbringing.[23]

In psychological and emotional terms, it is known that a better adequacy to the designated sex indicates less presence of conflict with the genital anatomy and presupposes a development of gender identity consonant with it. The role of parents in this construction is fundamental, because they are responsible for the child's First relations with the external world, projecting in it their references about their sexual identity and their “foundations” in the construction of gender identity.[23]

After the discovery of the etiology of DSD, a meeting of the multidisciplinary team that evaluated the case with the parents of the NB should take place, in which the diagnosis, its prognosis and the association of both with the definition of sexual identity are discussed. At that same meeting, the team must expose parents to a treatment plan, which usually involves hormone therapy and surgeries.[23,24]

It is important that parents have space to bring their doubts and anxieties, which should be discussed with the professionals of the team, as well as that they can participate in the decisions from the information offered by the team. Surgery to correct the genitalia before the first year of life is a controversial issue and much discussed by the reference centers that assist this population. However, among the scientific community, the defense of sexual attribution at birth, complemented by early surgical interventions and education consistent with the designated sex, still prevails. This process assists families and patients themselves in building their psychosocial issues.[23,24]

For the psychologist who works with these patients, it is essential to understand that DSDs, as a large group of genital malformations of various etiologies should be seen as clinical conditions. If there is this perception, the help to parents, at first, and to patients, later, will be to promote a greater naturalization of the treatment process, aiming at adequate adherence and a better quality of life throughout the development of these individuals.[25]

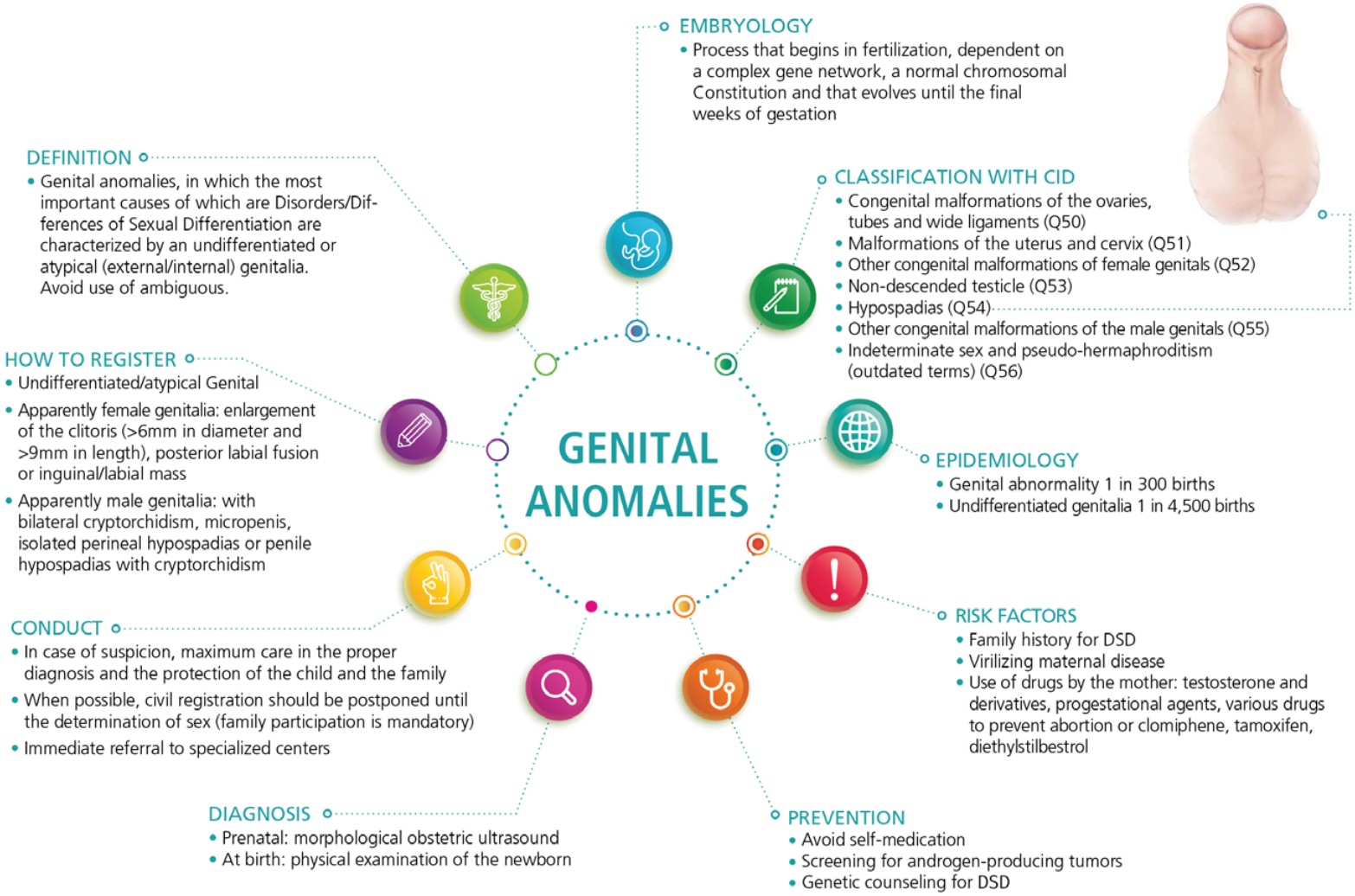
HOW TO REGISTER?

Genital anomalies, as well as other congenital anomalies identified at birth, must be registered in the Live Birth Certificate (DNV), by filling in fields 6 and 41. In the coding step, hypospadias must be registered with the CID code- 10:Q54, while the DDS with ICD-10:Q56. Special attention should be given to filling in the variable "Sex" (field 3) of the DNV, as the alternative "Ignored" should only be checked in cases of DDS.[25]

TO REMEMBER

- Disorders of sexual differentiation (DSD) should be adequately identified, registered and monitored in a tertiary hospital by a multidisciplinary team from birth until after treatment.
- The following frames are framed as undifferentiated external genitalia:
  - Obvious genital undifferentiation.
  - Apparently female genitalia with an increase in the phallus, fusion of labioscrotal protrusions or mass in the inguinal region/ labioscrotal protrusions.
  - Apparently male genitalia with bilateral non-palpable gonads, urethral meatus/ perineal urogenital sinus isolated, or non-topical urethral meatus with non-palpable gonad.

INFOGRAPHIC



Source: authors. Infographic/images - WHO/CDC/ICBD. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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7 CONGENITAL ANOMALIES OF THE LIMBS

SUMMARY

OBJECTIVE

To address topics of congenital limb anomalies, particularly limb reduction defects (LRD), clubfoot (talipes equinovarus), arthrogryposes and polydactyly.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

LRD are defined as the absence of an entire limb, or the absence and/or hypoplasia of parts of a limb, and may include the involvement of long bones, metacarpals and metatarsals and phalanges. The limbs have a complex embryonic development with a prolonged period of morphogenesis and exposure to the uterine wall larger than that of the body. These characteristics make the limbs more susceptible to malformations, deformations, ruptures, or other morphological variations. The prevalence rates of these defects have a huge variation, both between countries and between subtypes of defects, but on average it is 6-8/10,000 births. Proper registration of limb defects should discriminate the characteristics of the finding on physical examination, according to the definitions and classifications previously exposed, specifying the type of congenital anomaly, in which limbs are present, whether it is symmetrical or asymmetrical, whether it is isolated or associated with other congenital anomalies.

CONCLUSION

Limb defects can significantly affect the functional capacity and quality of life of affected individuals. In this sense, these conditions are of great relevance in the field of Public Health and their notification should be prioritized.

KEYWORDS

Congenital deformities of the limbs. Congenital deformities of the foot. Polydactyly. Arthrogryposis. Information systems. Surveillance in public health.

INTRODUCTION

Congenital anomalies of the limbs are characterized by the absence or severe hypoplasia of a full or part of the limb. The limbs have a complex embryonic development, with a prolonged period of morphogenesis with exposure to the uterine wall greater than that of the body. These characteristics make the limbs more susceptible to malformations, deformations, ruptures, or other morphological variations. A significant number of genetic and teratogenic conditions (medications, infections) affect the limbs in some way.[1,2]

Often the limb defect is part of a much more complex syndrome. About half of the cases of limb defects occur associated with other anomalies, leading to the need for a thorough search for other anomalies in all body systems.[1,3]

Different causes have already been identified for congenital limb anomalies. These abnormalities include genetic changes such as chromosomal changes, environmental exposures related to the use of drugs such as thalidomide and misoprostol, or infections such as by the Zika virus.[2,4]

In the early 1960s, several contries reported an epidemic of serious birth defects, particularly those related to the limbs, caused by the use of thalidomide. This epidemic highlighted the role of environmental teratogens in congenital anomalies and limb development.[5] The commercialization of thalidomide was prohibited worldwide, but the use of this drug still occurs for the treatment of leprosy erythema nodosum and other diseases in countries such as Brazil. However, the use of thalidomide is conditioned by the definition of clinical protocols and therapeutic guidelines with prescription and dispensing control criteria approved by the competent federal authorities. Despite these measures, there is a new generation of thalidomide survivors and Brazil is the only country in the world with three generations of thalidomide victims, with records until the year 2010. The occurrence of these cases is associated with the use of this drug, particularly in regions with high leprosy endemic and a large number of unplanned gestations.[6-8]

The severity of congenital limb anomalies presents high variability with certain phenotypes classically associated with particular etiologies.[4] In this sense, several attempts have already been made to systematically classify limb anomalies based on morphological, anatomical and etiological criteria. Most of them include deficiencies defined by their relationship to the central axis of the arm and leg: preaxial defects, central deficiencies and postaxial defects. The Live Birth Information System (Sinasc) in Brazil uses the International Classification of Diseases (ICD-10) to encode limb anomalies.

This chapter will describe the state of the art on congenital limb anomalies, particularly limb reduction defects (LRD), clubfoot, arthrogryposis and polydactyly.

EPIDEMIOLOGY

The general prevalence of congenital limb anomalies may vary, depending on variations in case definitions, inclusion/exclusion criteria, classification and sources of Investigation.[9] Although severe congenital limb anomalies are rare, in many cases they cause a reduction in the functional

capacity and quality of life of the affected individual.[10] This book will have a specific chapter on the epidemiology of congenital anomalies that will describe in more detail this topic.

Regarding limb reduction defects, the prevalence rates vary greatly, both between countries and between subtypes of defects, but on average it is 6-8/10,000 births.[3] In Brazil, a prevalence of 1.6/10,000 was recorded, being higher in the states of Pernambuco, Paraná and Rio de Janeiro. In a study, a relationship was observed between the prevalence of limb reduction defects and thalidomide dispensing.[11]

Clubfoot (*talipes equinovarus*) also has a variable prevalence among studies and populations, being higher among Indigenous people and lower among Asians. The highest rate found was in Indigenous peoples inhabiting the islands of Polynesia, (6.8/1,000 live births)[12] and in India (4.56/1,000). In the Americas the rate stands at 1.74/1,000.[13]

Arthrogryposis is part of several disorders, making it difficult to determine its prevalence. Lowry and collaborators[14] raised the numbers of some studies and found prevalence of multiple congenital contractures ranging from 0,08-0,30/1.000 births. There does not seem to be difference in the distribution between sexes, except for X-linked recessive forms.[14,15] Already for the most common type of Arthrogryposis, amyoplasia, was an estimated incidence of 1/10, 000 births.[16] Congenital Zika Syndrome contributed to the increase in the prevalence of this anomaly after 2015 in countries where there were outbreaks of this viral infection.

Among the limb defects included in this chapter, the most common are polydactyly. Castile and collaborators[17] found prevalence of polydactyly ranging from 6-15/10,000 live births, depending on the ethnic origin of the population. Other genetic factors also influence their prevalence, leading to variation in these numbers according to affected members and digits, polydactyly subtypes and sex.

EMBRYOLOGY

Limb development is a process that begins early in embryogenesis. This process is complex, as it involves several signaling pathways and regulations. Signals for limb formation are started around the 21st day after fertilization (Chart 1).[18]

The bud of the member has three main axes, which are responsible for the direction in which the members will be formed. The formation of the near-distal axis occurs from the first to the fifth digit, while from the ventral dorsal axis occurs in the direction from the back of the hand to the palm, and the anteroposterior axis is oriented from the shoulders to the digits.[19,20] In addition to the direction of the axes, the pattern of embryonic development of the upper limbs causes differentiation from the most proximal to the most distal structures, starting with the differentiation of the part of the arm that contains the humerus, followed by the forearm with the radius and ulna, wrist and finally the hand.[20]

In six weeks after fertilization, the hands and feet begin to become apparent, and the shoots go through a constriction forming the fists.[21] The formation of the hands and feet occur at different times, and the hands have their early development at the feet. Digital rays appear on the hands on day 41, while on the feet they will only be apparent on day 46.[18] The separation of the digits

of the hands occurs from day 46 and will occur in the feet only on day 49, being regulated by a process of programmed cell death. On day 56, the separation of the digits of the hands and feet is complete.[18,20]

The full development of the limbs is important in the formation of the skeleton, muscles and innervation. In the fifth week the processes of chondrification of the limbs, the cartilage skeleton will be formed and will be complete at the end of the sixth week of gestation, around day 58.[18,22] Also in the fifth week, the peripheral nerves begin their growth in the mesenchyme of the limbs. The process of innervation of the bud occurs by growth of the nerves of the ventral primary branch that will be distributed by the musculature in formation.[18] In addition, the process of angiogenesis is fundamental for the normal formation of the limb. The formation of blood vessels follows the formation of the bud, beginning the development of the arterial system on Day 33.[20]

For the formation of the limbs to occur on a regular basis it is necessary a very resistant control, due to the fact that it depends on several processes because it is an organ formed by many structures, having more than 30 bones and 50 muscles.[23] The main regulation is done by a genetic control network involving many genes expressed and important during development, such as homeobox (Hox), sonic hedgehog (SHH) and fibroblast growth factors (FGFs) genes.[21] In addition to genetic controls, limb development is also subject to the control of mechanical forces, which aid in the correct formation of limb bones, especially long bones.[24]

The imbalance of these processes can lead to problems of formation in the limbs leading to the development of malformations. The critical period of limb development for insults of environmental origin is considered from the 24th to the 36th day after conception.[18]

Chart 1 – Main milestones of limb development in humans[18,20-22]

PERIOD OF DEVELOPMENT (GESTATION DAYS)	DEVELOPMENT MILESTONES
21	Start of signaling
26	Visible upper bud
28	Visible lower Bud
33	Beginning of the arterial system of the limb; mesenchy-mal beginnings of bones (cartilages)
41	Digital rays appear on the hands; muscular system of the limbs is already developing
44	Digital Rays still connected by membrane
46	Digital rays appear on the feet; digital grooves appear on the hands
48	Flexion of the limb at the elbow
49	Digital grooves appear on the feet
52	Complete separation of the digits of the hands
56	Complete separation of the digits of the feet

Source: authors.

DEFINITION AND CLASSIFICATION

Limb reduction defects

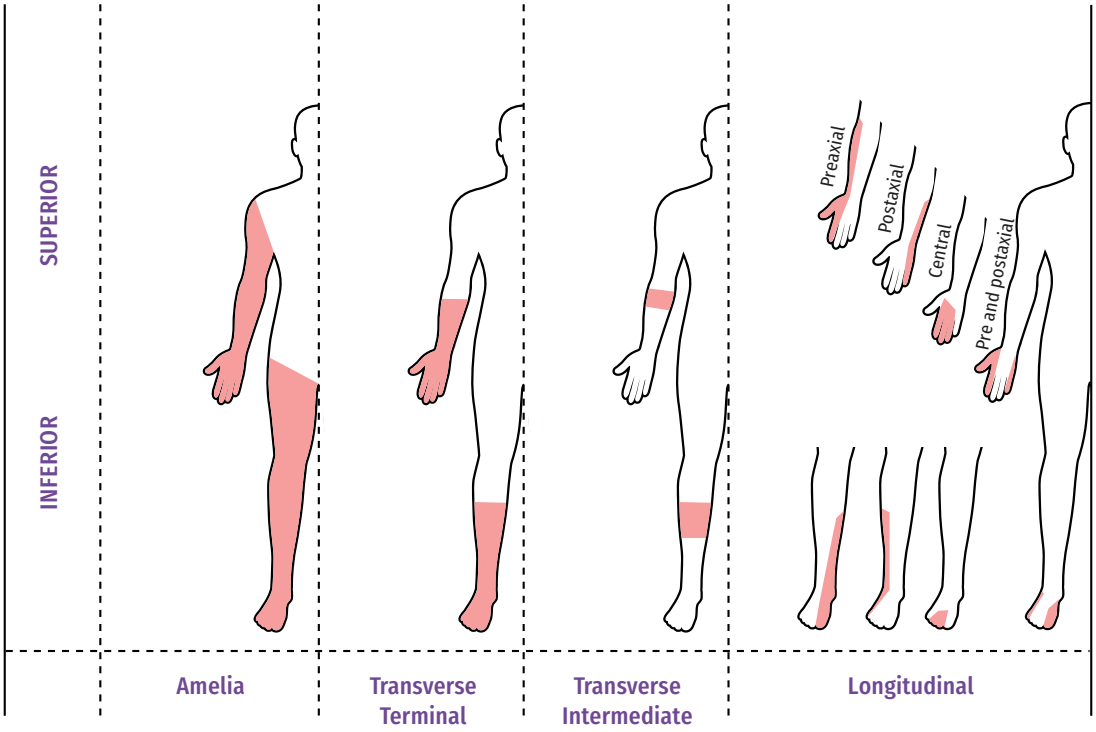
Limb reduction defects are defined as the absence of an entire limb, or the absence and/or hypoplasia of parts of a limb, and may include long bones, metacarpals and metatarsals and phalanges.[4] The classification of these defects was recently changed: in the past, Greek and Latin terms such as ectrodactyly, peromelia and phocomelia, among others, were used, which could often cause classification errors and confusion among the different evaluators.[25]

Several classifications have been proposed in the literature, but today it is recommended to classify according to Gold et al.,[4] which aims to provide a global idea of the defect in question, in a broad, simplified and effective way through anatomical classification. Thus, it is first defined whether the affected limb is totally absent, that is, agenesis of an entire limb, which is classified as "amelia"; or if the reduction defect affects only part of the limb, being classified as “meromelia”.

Meromelias can also be subdivided according to the orientation of the defect, into transverse or longitudinal. The transverse meromelias have by definition the involvement of all the axes of the limb and can also be divided into intermediate (defect occurs between two healthy portions of the limb) or terminal (defect occurs from one point to its distal end of the limb, with healthy portion of the limb only proximally). In compensation, longitudinal defects are defined as defects that do not affect all axes of the limb and are classified according to the axis affected; therefore, preaxial to the axis of the radius and tibia, postaxial for the ulna and fibula and central axis when the axes of the 2nd, 3rd and 4th digits are affected (Figure 1).

Phocomelia, as it was once called, is now recommended to be named or classified as an intermediate reduction defect of the arm, forearm, thigh and leg with the preservation of the hands and feet bilaterally. Similarly, ectrodactyly and peromelia are today classified as central longitudinal meromelia-type limb reduction defect and transverse terminal meromelia-type limb reduction defect, respectively.[25]

Figure 1 – Classification of reduction defects of the upper and lower limbs. Absent or hypoplastic structures are shaded



Source: figure elaborated by the authors, from the classification of Gold and collaborators.[4]

CLUBFOOT

Congenital clubfoot is a sign and not a diagnosis, being defined as a non-manually correctable deformity that affects both the foot and the ankle and leg of an individual.[26] The presence of these four structural changes is characteristic: the hollow foot, with its anterior portion in adduction and posterior rod, and the equine ankle (Figure 2).[27,28] Congenital clubfoot should be characterized if the involvement is unilateral or bilateral, as well as if it is isolated or if it is associated with other malformations or syndromes.

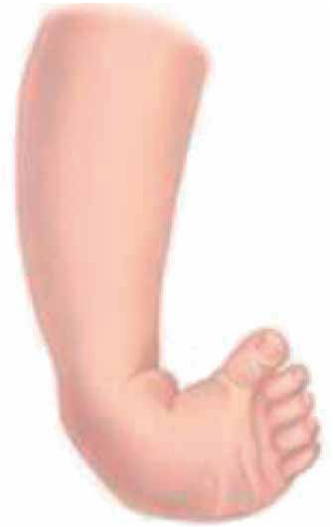
Congenital clubfoot can be classified in several ways, as to severity, etiology, genetics or limb functionality, as well as there are some severity scores described in the literature.[29,30] For clinical practice, classifications according to severity and according to etiology are useful.

According to the severity, congenital clubfoot can be classified into four categories:[31]

- **Grade 1** – benign, reducible without resistance.
- **Grade 2** – moderate, reducible with some degree of resistance.
- **Grade 3** – severe, reducible with higher strength.
- **Grade 4** – very severe, not reducible.

Regarding the etiology, congenital clubfoot can be classified into postural (usually the most benign and easy to treat), idiopathic (difficult to reduce, but usually isolated and not associated with syndromic causes), neurogenic (usually associated with neural tube defects) and syndromic (when associated with other malformations).[32]

Figure 2 – Congenital clubfoot



Source: WHO; CDC; ICBDSR. **Birth defects surveillance**: atlas of selected congenital anomalies. Geneva: WHO, 2014.[28]

ARTHROGRYPOSIS

Arthrogryposis is a sign, not a diagnosis, and is defined by the presence of multiple joint contractures, either in flexion or extension, causing limitation of joint movement. Arthrogryposis usually involves the limbs but can also involve the joints of the oropharynx and spine and must be present from birth.

There are several syndromes or sequences of arthrogryposis, but invariably all of them have reduced fetal movement, culminating in reduction of articular skin folds, presence of dimples on the affected joint and hypotrophy, in addition to a course of the disease that is usually static and not progressive.[14] More than 400 syndromes including arthrogryposis have already been clinically described, and about 150 have already been found, and several others have already been attributed to environmental or teratogenic causes.[15]

Due to the enormous heterogeneity, the classification of these conditions becomes a challenge. Hall, in his 2007 book subdivided arthrogryposes into three distinct categories, which can assist in the search for an accurate etiological diagnosis:[16]

A member involvement only;

B involvement of members and other structures; and

C neuromuscular involvement associated with central neurological changes; or intellectual disability.

POLYDACTYLY

Polydactylies are a group of most common and generally easily identifiable limb defects, but their definition and classification sometimes leave doubts. This defect has by definition the presence of a supernumerary digit,[33] which can be present in a complete or partial way, being able to reach both the upper and lower limbs, and can be present in only one limb or even in the four limbs simultaneously. In addition, polydactyly can be isolated or be part of syndromic diagnoses.[34]

The essential classification of polydactyly is according to the axis affected (preaxial, postaxial and central) and according to the presence of the integer (complete) or partially (partial) digit. In relation to the affected axis, the preaxial polydactyly is the most common and occur when the supernumerary digit is, in fact, a doubling of the hallux, and this doubling can be complete or incomplete, that is, it can vary from only the tip of the duplicated distal phalanx to the duplicated digit integrally.

"Postaxial" polydactyly is that in which the doubling of the fifth digit occurs, and the phenotype can vary from only an appendix without recognizable bone structures, to the complete doubling of the fifth finger. Central polydactyly is much rarer than pre or postaxial polydactyly and is usually masked by the presence of a syndactyly, being usually recognized as polysyndactyly.[34] There are also specific subclassifications for each affected axis, according to the duplicate portion that will not be addressed in this manuscript, but that can be found in Wessel et al.[35]

RISK FACTORS AND PREVENTION

The risk factors for the occurrence of limb anomalies are environmental and genetic. The main environmental factors include teratogens such as thalidomide drugs, misoprostol, Zika virus infection, as well as mechanical factors such as amniotic fluid reduction. Among the numerous genetic factors, many chromosomal changes and gene syndromes are included, and it is also important to mention African ancestry as a risk factor for non-syndromic postaxial polydactyly, which has no clinical repercussions and is easy to manage on an outpatient basis.[18]

Thus, its prevention largely involves the control of environmental factors and pregnancy planning, as will be seen in the specific chapter in this volume.

MANAGEMENT OF THE PATIENT WITH LIMB DEFECT

The management of the patient with congenital limb defects should be multidisciplinary. The recommended team includes pediatricians, neonatologists, geneticists, orthopedists, pediatric surgeons, physiotherapists, psychologists and nurses. In addition to examining the defect primarily, it is important to evaluate the newborn as a whole, looking for signs and symptoms that can corroborate with a syndromic diagnosis, since the limb defect can be considered a marker of other genetic problems.

Stoll and collaborators[3] and Stevenson and collaborators[1] stated that about half of the cases of limb defects occur in association with other anomalies, reinforcing the need for a thorough search for other anomalies in all body systems. Also, whenever possible, it is indicated to perform additional radiological examinations, mainly the radiography of the limbs for better classification and definition of the congenital defect.

FINAL CONSIDERATIONS

The limbs have a complex development, a prolonged period of morphogenesis and exposure to the uterine wall greater than that of the body. These characteristics make the limbs more susceptible to malformations, deformations, ruptures, or other morphological variations. Limb defects can significantly affect the functional capacity and quality of life of patients. Therefore, the diagnosis, treatment and follow-up of patients should be carried out by a multidisciplinary team in the most effective way possible to mitigate the possible damages.

HOW TO REGISTER

Proper registration of limb defects should discriminate the characteristics of the finding on physical examination according to the definitions and classifications previously exposed, specifying the type of congenital anomaly, in which limbs are present, whether it is symmetrical or asymmetrical, whether it is isolated or associated with other congenital anomalies. Chart 2 shows the list of ICD codes related to these anomalies.

Chart 2 – ICD-10 code list of congenital limb anomalies reported in this chapter, with their correspondence to the classification of Gold and collaborators,[4] in the case of limb reduction defects

ICD-10CODES FOR LIMB ANOMALIES	
LIMB REDUCTION DEFECTS	
CLASSIFICATION PROPOSED BY GOLD AND COLLABORATORS[4]	ICD-10 CODE
	Q71 Upper limb reduction defects
Complete absence of the upper limb (amelia)	Q71.0 Complete congenital absence of the upper limb(s)
Intermediate defect	Q71.1 Congenital absence of the arm and forearm, with present hand
Transverse terminal defect	Q71.2 Congenital absence of forearm and hand
Transverse terminal defect	Q71.3 Congenital absence of hand and finger(s)
Preaxial longitudinal reduction defect	Q71.4 Radio longitudinal reduction defect
Postaxial longitudinal reduction defect	Q71.5 Ulna longitudinal reduction defect

To be continue

Conclusion

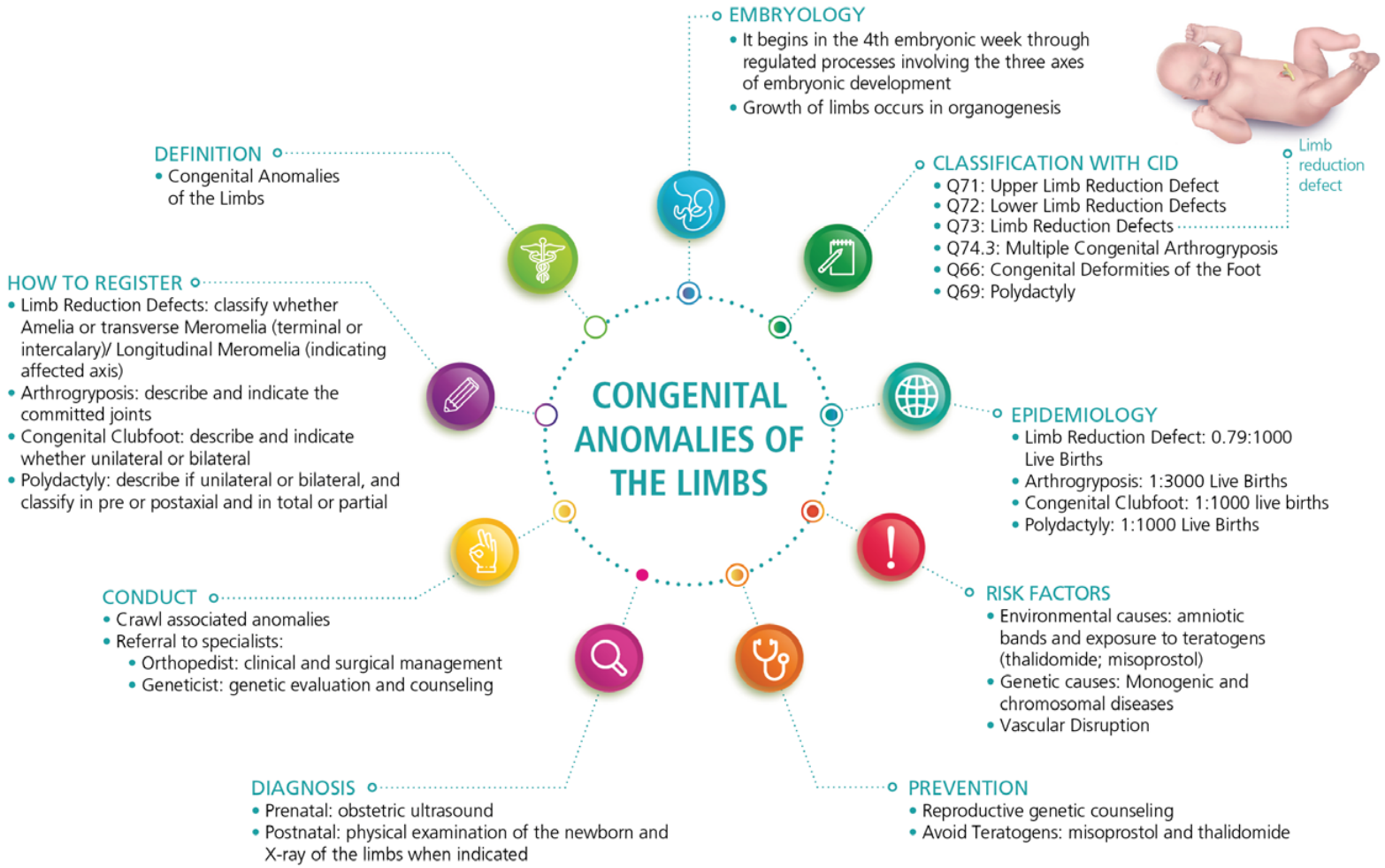
ICD-10CODES FOR LIMB ANOMALIES	
LIMB REDUCTION DEFECTS	
CLASSIFICATION PROPOSED BY GOLD AND COLLABORATORS[4]	**ICD-10 CODE**
Central longitudinal reduction defect	Q71.6 Hand in lobster claw
	Q71.8 Other upper limb reduction defects
	Q71.9 Upper limb reduction defect, unspecified
	Q72 Lower limb reduction defects
Complete absence of the lower limb (amelia)	Q72.0 Complete leg absence of lower members
Intermediate defect	Q72.1 Congenital absence of thigh and leg with foot present
Transverse terminal defect	Q72.2 Congenital absence of leg and foot
Transverse terminal defect	Q72.3 Congenital absence of foot and toes
Preaxial longitudinal reduction defect	Q72.4 Defect by longitudinal reduction of the femur
Preaxial longitudinal reduction defect	Q72.5 Defect by longitudinal reduction of the tibia
Postaxial longitudinal reduction defect	Q72.6 Defect by longitudinal reduction of the fibula
Central longitudinal reduction defect	Q72.7 Bifid foot
	Q72.8 Others defects by reduction of lower members
	Q72.9 Unspecified defect by lower limb reduction
	Q73 Unspecified limb reduction defects
	Q73.0 Congenital absence of unspecified limbs
Intermediate defect	Q73.1 Phocomelia, members not specified
	Q73.8 Other defects by reduction of unspecified members
OTHER LIMB ANOMALIES	
Q66.0 – Equinovar clubfoot	
Q69 – Polydactyly	
Q69.0 – Supernumerary hand fingers	
Q69.1 – Supernumerary thumbs	
Q69.2 – Supernumerary Toes	
Q69.9 – Polydactyly not specified	
Q74.3 – Multiple congenital arthrogryposis	

Source: CID-10 y Gold y colaboradores[4].

TO REMEMBER

- Congenital anomalies of the limbs are characterized by the absence or severe hypoplasia of a limb or part of it, the presence of an extra digit, or the change in mobility and articular positioning of one or more limbs.
- Limb defects can significantly affect the functional capacity and quality of life of patients.
- Embryonic development of the limbs is an important example of complexity of human embryogenesis and the many factors that may contribute to the occurrence of congenital anomalies.
- Diagnosis, treatment and follow-up of patients should be carried out by a multidisciplinary team in the most effective way possible to mitigate possible damage.

INFOGRAPHIC



Source: authors. Infographic/images - WHO/CDC/ICBD. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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8 ABDOMINAL WALL DEFECTS

SUMMARY

OBJECTIVE

To address topics on abdominal wall defects, describing their occurrence, embryological formation, characterization, classification, epidemiology, management and appropriate forms of registration.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

Embryological mechanisms involving abdominal wall defects to this day remain controversial. Through the improvement in prenatal care, including advances in imaging tests, especially obstetric ultrasound, currently, newborns with these malformations have a good prognosis in their rehabilitation. It should be noted that omphalocele is often associated with other malformations in up to 70% - 80% of cases and may be part of a genetic syndrome. It is important to consider that such factors change the clinical prognosis. Gastroschisis usually occurs in isolation, except for malformations of the intestine itself, such as atresia or stenosis. Environmental risk factors and genetic susceptibility are indicated as triggers of these defects. Gastroschisis has the particularity of being associated with very young maternal age. In addition, gastroschisis showed an increase in its incidence of 10 to 20 times in the last decades, since the 1970s, while omphalocele remained with its stable incidence.

CONCLUSION

Detailed epidemiological data on abdominal wall defects in Brazil are necessary for adequate allocation of resources in order to reduce morbidity and mortality through affordable and quality care. In this sense, they are conditions of great relevance in the field of public health and their notification should be prioritized.

KEYWORDS

Congenital abnormalities. Gastroschisis. Exonphalia. Omphalocele. Information systems. Surveillance in public health.

INTRODUCTION

Knowledge about the etiology and management of abdominal wall defects was extremely scarce until the early 1940s. Mortality at that time was close to 100%. There was no clear distinction between these types of congenital anomalies. Since then, many studies for adequacy in the classification and management of these defects have been conducted. The knowledge acquired through the identification and analysis of newborns with congenital malformations is fundamental for understanding morphogenesis in humans and for the evolution towards the definition of genetic markers associated with the occurrence of such defects.[1] Advances in prenatal diagnosis, peri and neonatal care, as well as the identification of risk factors, have significantly decreased the morbidity and mortality of newborns with abdominal wall defects in the last 30 years.[2] The recognition of the malformation and the care by multi-professional team at birth are the main factors that affect the prognosis.[3]

DEFINITION

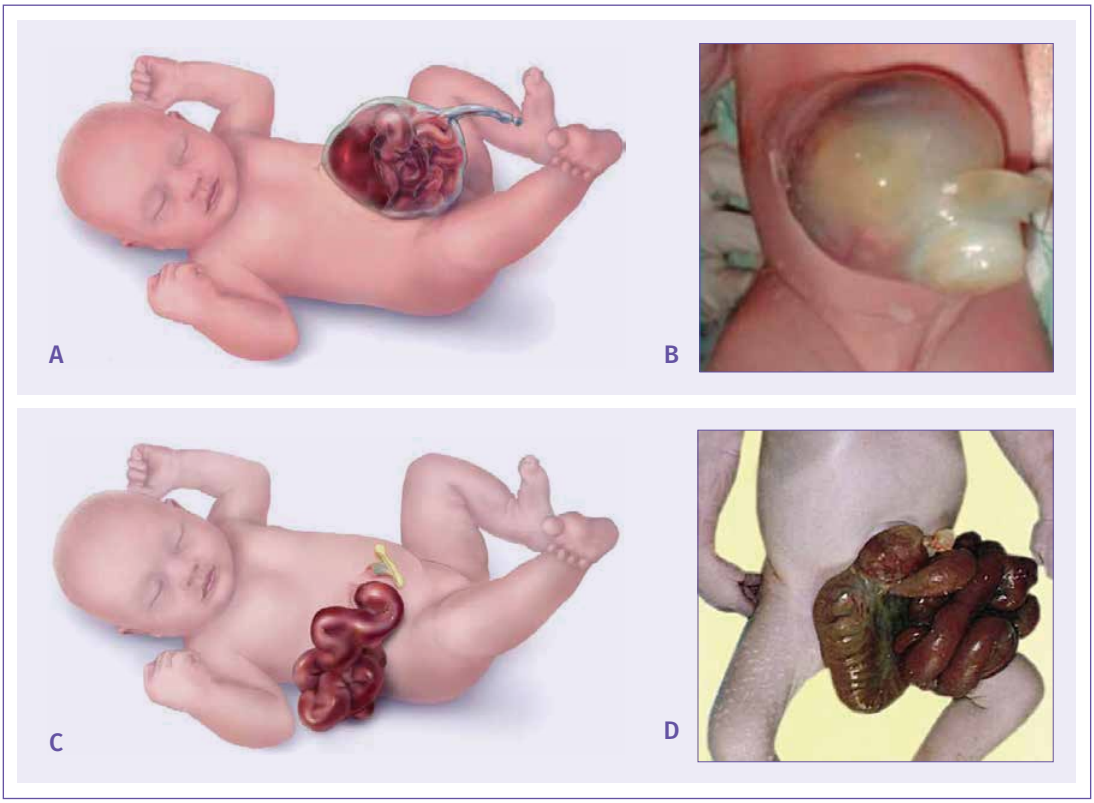
Congenital defects of the abdominal wall result in protrusion of intra-abdominal organs, mainly intestine.[4] They are relatively frequent, especially omphalocele and gastroschisis.[5,6]

Omphalocele or exonphalia is a defect of closure of the anterior abdominal wall that occurs through the umbilical ring, resulting in exteriorization of the abdominal contents, covered by a membrane that may or may not be intact.[7] In addition to the intestine may contain liver, spleen, and eventually gonads. Giant omphaloceles are associated with hypoplasia of the pulmonary and rectus abdominal muscles (laterally displaced).[8–10] Often associated with other congenital malformations, omphalocele may be part of genetic syndromes, most commonly aneuploidies and Beckwith-Wiedemann syndrome.[10]

Gastroschisis is characterized by discontinuity of the abdominal wall in the paraumbilical region, almost exclusively on the right (95% of cases), through which there is exteriorization of intestinal loops, and occasionally other organs, not enveloped by the typical membrane of gastroschisis.[1,7,11] Exposure of the intestinal loops in the intrauterine period causes edema of the intestinal loops observed at birth.[12] It is usually an isolated defect, except for gastrointestinal malformations.

Rupture of the hernial sac, present in the omphalocele, can occur very rarely in the intrauterine period. In these cases, confusion with gastroschisis is observed, since the intestinal loops are exposed at birth. It is worth noting that omphalocele, even when routed, has umbilical cord insertion in the membrane that surrounds the exteriorized organs, that is, this cord is part of the defect and is looser than usual, while in gastroschisis the umbilical cord is normally inserted in the abdominal wall next to the defect. Umbilical hernia is characterized by habitual insertion of the cord into the umbilical ring with intact skin cover, while in the omphalocele there is a large defect of the umbilical ring area without muscles or skin, only a thin membrane (Figure 1).[8,13]

Figure 1 – A and B: illustrative drawing and photography of newborn with omphalocele. C and D: Illustrative drawing and photography of newborn with gastroschisis



Source: adapted from WHO; CDC; ICBDSR. **Birth defects surveillance**: atlas of selected congenital anomalies. Geneva: WHO, 2014.

EMBRYOLOGY

The embryology of abdominal wall closure defects remains controversial, only very recent studies seem to offer more well-supported explanations. Various theories include failures in the formation of the abdominal wall.[14,15] The mechanism by which this failure occurs is not well elucidated. Among the challenges to such understanding is the limited availability of experimental models.[1,16,17] In embryonic development, the umbilical cord can be divided into two parts: left side (vascular part) and right side (flabby "bag" - shaped part), in which the intestinal loops will develop.

Physiological herniation of the intestinal loops in the flaccid hiatus resolves by the 11th to 12th week of gestation. As in gastroschisis, the physiological hernia is usually located on the right side of the umbilical cord and this is well fixed, with normal length and morphology. This fact suggests an association of physiological hernia with the occurrence of gastroschisis. To date it is not defined whether the prolapse of the viscera in the gastroschisis is due to failure to close the umbilical ring before the resolution of the physiological herniation or the rupture of the flaccid part at the edge of the ring.[18-20]

Embryogenesis of omphalocele involves a combination of embryonic dysplasia and ectodermal plaque dysfunction.[21] In omphalocele the umbilical ring is abnormal and enlarged. During normal development the ring closes until it reaches the same circumference of the umbilical cord, thus the mature abdominal wall covers the surrounding ventral surface. In omphalocele the umbilical ring is larger than the place of insertion of the cord and the mature abdominal wall is limited to the periphery of the defect.[22]

CLASSIFICATION

Abdominal wall defects can be classified into two types of larger malformations:[23]

- **Omphalocele (exonphalia):** in this defect, the abdominal contents (intestine, for the most part, but also other abdominal organs) are herniated in the midline by means of an enlarged umbilical ring. The umbilical cord is inserted into the distal part of the membrane that covers this anomaly. Herniated organs in the omphalocele are covered by a membrane consisting of the peritoneum and the amnion. The international code of this malformation corresponds to ICD-10:Q79.2.
- **Gastroschisis:** anomaly accompanied by herniation of the intestine and occasionally other abdominal organs. The opening in the abdominal wall is lateral to the navel (on the right in 95% of cases), and the herniated organs do not have a protective membrane. The international code of this malformation corresponds to ICD-10:Q79.3.

EPIDEMIOLOGY

Gastroschisis is a congenital malformation with increasing rates of occurrence in recent decades, observed in geographical regions with low and high socioeconomic level.[24] The incidence in live births is estimated between 2 to 5 cases per 10,000 live births.[4,25] One of the main risk factors for gastroschisis recognized in several studies is the young maternal age (especially between 15-19 years).[6,26] Pregnant women under the age of 20 may have up to seven-fold increased risk for gastroschisis in the developing fetus when compared to those aged 25-29 years.[27]

For omphalocele, a prevalence of 1 in 4 thousand live births is estimated. However, the incidence is higher if stillbirth and gestational interruptions are considered.[28] Syndromic omphalocele, with detectable chromosomal abnormalities or associated congenital anomalies, represents 67%-88% of pregnancies with this malformation.[29] The associated congenital anomalies are mostly gastrointestinal or cardiac (40%-50%), but a wide spectrum of associations may occur.[28,30] Omphalocele mortality rates often vary based on the pattern of associated malformations or syndromic diagnoses. Omphalocele alone seems to have a good prognosis.[31]

In Brazil, specific studies related to these congenital malformations are still scarce. However, the rates seen in the country are similar to those described worldwide and follow the same epidemiological trends and risk factors of other geographic regions.[7] Updated Brazilian epidemiological data are addressed in the epidemiology chapter of this book.

RISK FACTORS

The occurrence of abdominal wall defects involves multiple environmental and genetic factors, which can have an impact independently, but most often interact with each other for an increased risk.[32]

Risk factors for omphalocele include advanced maternal age (>35 years) or very young (<20 years).[33] Obesity also seems to be important, especially for mothers with BMI> 30[34] or previously obese at pregnancy (BMI ≥30).[35] In addition, maternal glycemic control disorders have also been identified as a potential risk factor for omphalocele development.[36]

However, genetic variants and chromosomal abnormalities are the main risk factors associated with this condition, in particular trisomies of chromosomes 21, 13 and 18;[32,37] the latter being the most observed, since up to 80% of Edwards syndrome cases present omphalocele.[38] Beckwith-Wiedemann syndrome is another condition associated with increased risk of omphalocele, which occurs in 30%-79% of these patients.[39] In about 30% of cases omphalocele occurs in isolation and with normal karyotype, with a favorable prognosis (survival greater than 95.5% in the first year of life).[40]

Gastroschisis has very different epidemiological characteristics compared to omphalocele, and it is rarely associated with chromosomal abnormalities (1.2% of cases) or monogenic diseases (0.2%).[41] However, it is also associated with young maternal age: women between 14-19 years have up to seven times more risk when compared to women between 25-29 years (OR=7.18, 95%CI: 4.39-11.75).[27] Several environmental and sociodemographic factors have already been associated with increased risk in its occurrence, among them: young paternal age, low income and low educational level, use of analgesics (aspirin, ibuprofen and paracetamol), smoking and nutritional factors,[42] but a number of limitations in these studies and significant variability between the results does not yet allow definitive conclusions about these factors. The increase in the frequency of familial cases of gastroschisis suggests a higher underlying genetic susceptibility (risk of recurrence ranges from 3.5% to 5.7%),[43,44] with some genetic variants of susceptibility already described.[45]

PREVENTION

Prevention of abdominal wall defects goes directly through maternal health care in the preconception period.[11] At this time, many of the risk factors can be identified and thus eliminated or mitigated, through measures such as weight reduction, smoking cessation, optimization of glycemic control in diabetic women and guidance on medication use.

Folic acid, an effective preventive measure in other congenital anomalies (especially neural tube defects), does not appear to have a significant impact on the incidence of abdominal wall defects.[46,47] In any case, by the benefits described above it is also indicated.

Proper ultrasound screening allows prenatal diagnosis of these conditions. Thus, it is possible to define the indication of invasive tests (chorial villus biopsy or amniocentesis), especially important in cases of omphalocele, with a view to the investigation of associated genetic conditions. These measures allow the health team and the family to plan the best conduct and care for the newborn in the immediate peripartum and neonatal period, through referral to the health service with a qualified surgical team, definition of the best delivery route or possible indication of early termination of pregnancy,[48] thus preventing complications of these conditions. This book has a specific chapter that presents in more detail the prevention of congenital anomalies.

PRE AND POSTNATAL DIAGNOSIS

Obstetric ultrasound is the method of choice for the diagnosis of abdominal wall defects, capable of detecting them in 75% to 80% of cases from the 11th to 12th weeks of gestational age. The elevation of alpha-fetoprotein is observed in both defects; however, it is more pronounced in omphalocele.[49] In the case of omphalocele identified in the prenatal period, etiological investigation can be followed with analysis of fetal karyotype, through amniocentesis, and/or chorionic villi sample.[50] The most comprehensive fetal evaluation should be followed, including echocardiography.[49]

With the advancement of quality in imaging tests, prenatal identification of both omphalocele and gastroschisis can now be done from the end of the first trimester through obstetric ultrasound.[19,51] In reference centers, it is possible to carry out the diagnosis of omphalocele between 11 and 14 weeks of gestation. This assessment should be quite careful before 11-12 weeks to avoid confusion with physiological umbilical hernia, this never includes herniation of the liver and must be resolved by 14 weeks of gestation.[51,52] Gastroschisis can be identified from 12 weeks.[19,52]

There are not enough data to support the choice of the best delivery route, therefore, this is a choice of the doctor together with the mother and the factors evaluated become the obstetric ones. In gastroschisis, there are advocates of routine cesarean section, due to the risk of lesions of the intestinal loops during vaginal delivery; in omphalocele, some doctors prefer cesarean section when there is large omphalocele, for fear of rupture of the membrane that covers the viscera and liver damage during vaginal delivery. Regardless of the type of delivery chosen, it is essential to ensure that it takes place in a tertiary hospital, with trained neonatology and pediatric surgery team.[49]

HANDLING AND CONDUCT

Surgery is the therapy of choice when it comes to abdominal wall defects: gastroschisis and omphalocele. The main goal of the correction is the reduction of the viscera, with preserved functionality and subsequent closure of the abdominal wall. In gastroschisis surgery is considered emergency, while in omphalocele the closure may be later. About 2/3 of the deaths and sequelae acquired as a result of these defects could be avoided through appropriate surgical treatment to the affected babies and children.[53]

Surgical correction of the defect cannot be the only concern. Newborns with intestines and possibly other exposed viscera should be immediately evaluated for Gastrointestinal Motility, heat and fluid losses. Some specific care needs to be followed, such as the passage of nasogastric tube, volume replacement, hydration of the exteriorized contents with moist gauze with warm saline solution, maintenance of the newborn in a warm environment and breastfeeding in a right lateral position to avoid twisting of the mesenteric vessels.[54]

Despite advances, both in surgical techniques and neonatal care, it is not yet established what the best therapeutic approach for neonates with gastroschisis. There are three main techniques to make the closure: primary fascial suture after reduction of the viscera; staggered correction with the use of silo; umbilical turban technique or plastic closure. There is still no clear evidence demonstrating superiority of some of the techniques.[55] In addition, the therapy to be followed after surgery is challenging, with gastroschisis being the congenital malformation associated with longer hospital stay.

In omphalocele surgery is not considered emergency if there is no rupture of the membrane that surrounds the viscera. These steps are followed during surgery: the surrounding membrane is opened, the umbilical vessels are connected, flaps of skin are created for subsequent suturing of fascias, viable viscera are reduced, the created fascias are transversely closed and finally the bag suture is performed to obtain the navel. This closure cannot always be done at the same time; in this case, it is performed later by some available techniques, such as Gross technique, Schuster technique, sequential ligation with the use of silo, devices for tissue expansion and non-operative conservative therapy, in which the closure is expected only with the use of cream silver sulfadiazine and subsequently the residual hernia is corrected.[49]

HOW TO REGISTER?

Proper registration of abdominal wall defects should discriminate the characteristics of the finding. According to the Manual of the Latin American Collaborative Study of Congenital Malformations (Eclamc), it should be registered:[56]

- **A** the relationship with the umbilical cord (e.g. periumbilical);
- **B** the side;
- **C** the extension in centimeters;
- **D** if it is covered with membranes;
- **E** if there is a gutted organ; and
- **F** presence of association with independent malformation.

As an example, gastroschisis is usually located to the right of the umbilical cord, with exteriorization of part of the intestine not covered by membrane, being more commonly an isolated malformation. Omphalocele is located in the midline and the herniated organs are covered by a membrane and is often associated with other malformations.[57]

In the registration of these defects, the use of the term 'gastroschisis' should be used with caution, since, often, defects of closure of the ventral wall of the body are erroneously referred to in this way.[22,56]

FINAL CONSIDERATIONS

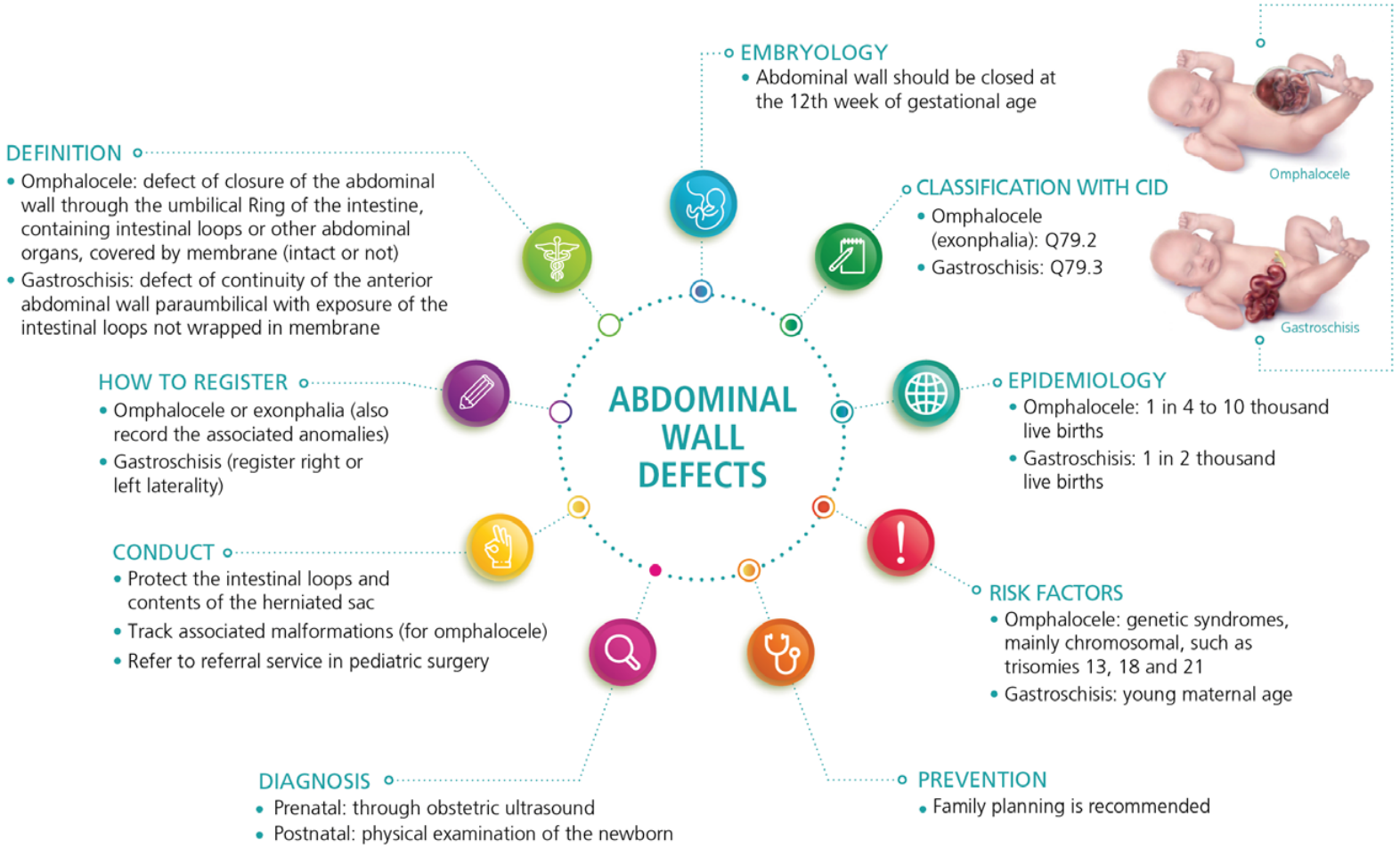
With the increase in the incidence of gastroschisis, the causes of this malformation should attract more and more attention.[22] Prevention through the promotion of maternal preconception health, associated with prenatal care, is relevant in this context.[11] In addition, mortality due to abdominal wall closure defects varies greatly with the quality of care, therefore, its correct and early identification, ideally prenatal, is of great importance, which makes it possible to plan delivery and appropriate neonatal care. In the presence of these anomalies, screening for other independent malformations and the development of an appropriate multidisciplinary care and rehabilitation plan are essential.[6,49]

In addition, in the context of abdominal wall defects, genetic counseling should be guaranteed to families since there are possible environmental factors acting on the occurrence of these malformations and that the maternal age both very young and advanced predisposes to different malformations.[6]

TO REMEMBER

- Defects of the abdominal wall have a wide spectrum of severity.
- Gastroschisis and omphalocele are the most common abdominal wall defects at birth.
- Omphalocele or exonphalia is a defect of closure of the anterior abdominal wall that occurs through the umbilical ring, resulting in exteriorization of the abdominal contents, covered by a membrane that may or may not be intact.
- Gastroschisis is characterized by discontinuity of the abdominal wall in the paraumbilical region, most often on the right (95%), through which there are exteriorization of intestinal loops, and occasionally other organs, not enveloped by membrane.
- The recognition of these defects in the prenatal period allows planning with specialized surgical team and, thus, the reduction of morbidity and mortality associated with these defects.
- When identifying malformations of the abdominal wall, it is essential to screening for other possibly associated malformations and the development of a multidisciplinary care plan and adequate rehabilitation.
- The correct classification, characterization and registration of abdominal wall defects at birth are essential for understanding local epidemiology, for identifying any associated risk factors, for establishing prevention measures and for genetic counseling.

INFOGRAPHIC



Source: authors. Infographic/images - WHO/CDC/ICBD. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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9 DOWN SYNDROME

SUMMARY

OBJECTIVE

To address topics related to Down syndrome (SD), describing its etiology, risk factors, clinical picture and methods for diagnosis, in order to help health professionals in recognizing this congenital syndrome.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

DS is the most common genetic disease that leads to intellectual disability and there are signs and symptoms that can be recognized at birth, as well as changes in prenatal care that allow suspicion. The existence of protocols for the care of patients with DS, with immediate interventions when necessary and tracking of possible health problems, makes it essential to recognize these patients as early as possible. In prenatal care, obstetric ultrasound is the main examination for suspicion of DS. It should be followed by risk assessment for all pregnant women, regardless of maternal age. After birth, physical examination of the newborn by an experienced professional allows diagnosis in most cases.

CONCLUSION

Surveillance of alterations suggestive of DS in the pre- and postnatal period increases the chances of early diagnosis and implementation of health measures in specialized centers, with a better quality of life for patients and their families. In this sense, this condition is highly relevant in the context of public health in Brazil and its notification should be prioritized.

KEYWORDS

Congenital abnormalities. Down syndrome. Maternal age. Information systems. Surveillance in public health.

INTRODUCTION

Down syndrome (DS) is the most common genetic cause of intellectual disability, with an incidence around 1:800 to 1:1,000 live births.[1,2] People with this condition have a set of signs and symptoms that, in most cases, can be readily recognized at birth. In addition, there are changes that allow the diagnosis even in the prenatal period, allowing the preparation of the health team and the family for possible complications.[3]

People with DS have delayed neuropsychomotor development and an increased risk for heart malformations, respiratory, visual, auditory, hematological, gastrointestinal, endocrinological and dental problems.[4] Early diagnosis of DS is possible and benefits patients from immediate interventions. For example, congenital heart abnormalities are present in about half of cases and contribute to morbidity and mortality.[5,6,7] Despite this, there is still a large number of patients who are investigated late, with a loss in their follow-up and clinical management.[8]

There are guidelines for the health care of patients with DS, with guidelines on the periodic evaluations necessary according to age and comorbidities, which must be followed for the best possible development of these people.[9]

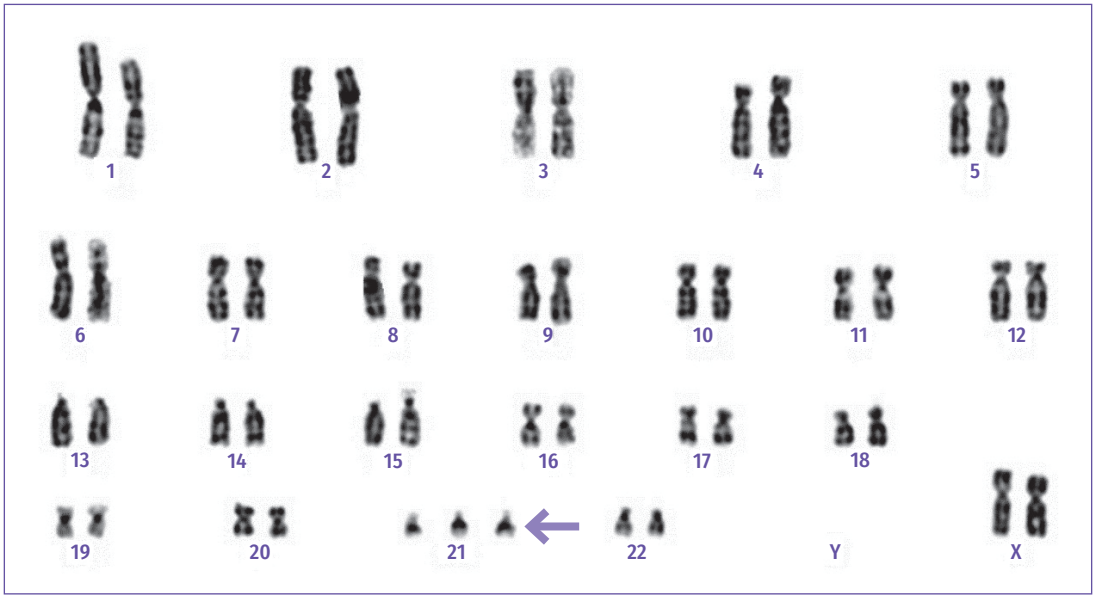
The discussion of surveillance strategies is important to enable the initiation of the recommended health follow-up. The objective of this chapter is to prepare the health professional for the prompt recognition of the signs and symptoms of DS. For this, we seek to discuss their etiology, risk factors, clinical picture and methods for diagnosis, aiming at clinical suspicion still in the prenatal period and the prompt identification of these patients at birth so that care measures are carried out as early as possible.

ETIOLOGY

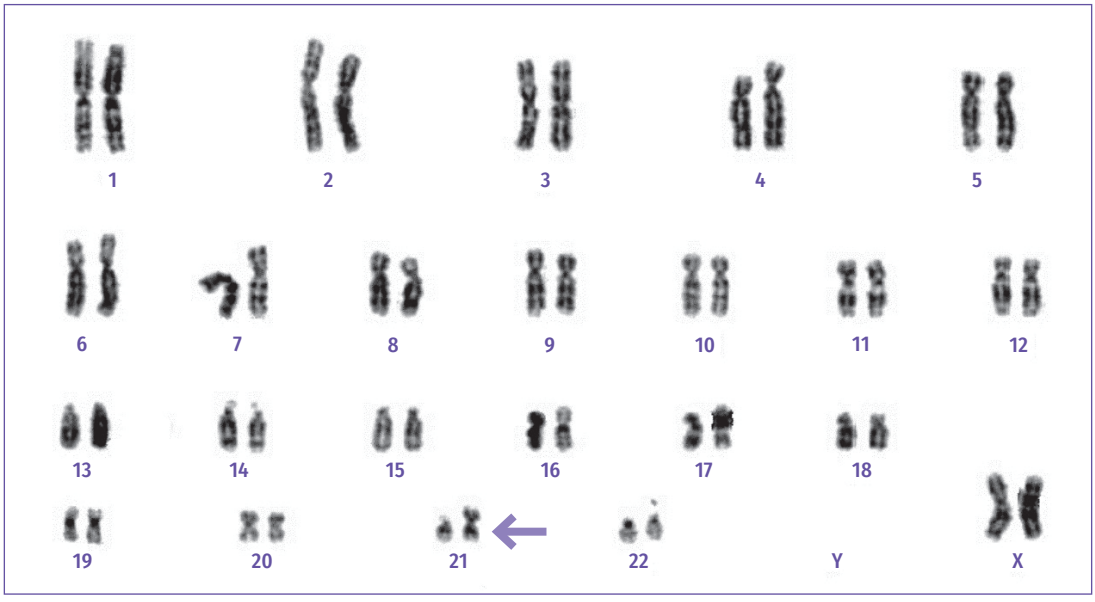
Approximately 95% of DS cases are sporadic and related to meiotic non-disjunction, resulting in a karyotype with 47 chromosomes instead of the usual 46, with one chromosome 21 more – the so-called free trisomy of chromosome 21 (Figure 1A). In about 90% of these cases, this failure in separation occurs in meiosis I of maternal oocytes.[10,11]

Familial recurrence may be related to structural changes involving chromosome 21. Among these changes are translocations, responsible for about 3% to 4% of DS cases and consisting of the fusion of the long arm of one chromosome 21 with the long arm of another chromosome of the acrocentric type (Figure 1B).[4] These patients have 46 chromosomes instead of the 47 chromosomes observed in free trisomy.[12]

Figure 1 – Examples of karyotypes of patients with Down syndrome. 1A: female karyotype 47, XX,+21 showing the free trisomy of chromosome 21. 1B: female karyotype 46, XX,+21, der (21;21)(q10;q10) showing trisomy of 21 by translocation



1A



1B

Source: authors.

In 1% to 2% of patients, the etiology is related to mitotic division in the early stages of embryonic development.[13] During cell division, more precisely during mitotic anaphase, a separation error involving the sister chromatids may occur resulting in two cell lines: one with a normal complement of 46 chromosomes and the other with 47.[14] This chromosomal change is the main cause of the so-called mosaicism, since from a single zygote two or more distinct cell lineages emerged.[13-15]

Other, rarer chromosomal changes account for a small percentage of DS cases. Among them is duplication involving the critical region of chromosome 21 and other structural changes involving this chromosome.[16]

RISK FACTORS

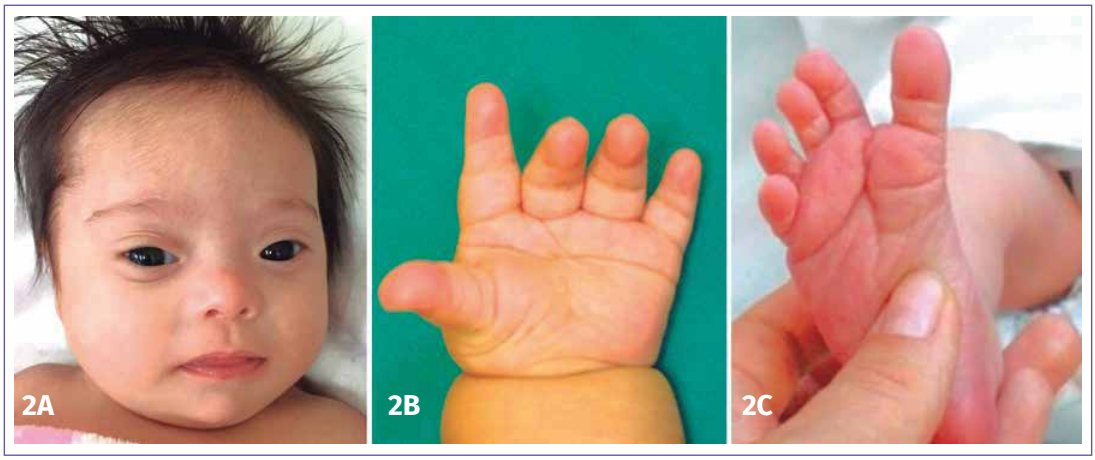
Considering the most common cause of DS, free trisomy of chromosome 21 by maternal meiotic non-disjunction, the only known risk factor is advanced maternal age.[17] As the oocytes get "older", the chances of dysjunctional defects are increased and, therefore, the chance of DS increases in proportion to the increase in maternal age.[18,19]

CLINICAL PICTURE

In the prenatal period, some characteristics observed in the first (US1T) and second trimester (US2T) ultrasound may suggest that the fetus has some chromosomal change. None of these are specific, but the combination with other clinical data, such as advanced maternal age, increases the relative risk, indicating the performance of other complementary tests. In US1T, the main findings include increased nuchal translucency (TN), absence or hypoplasia of nasal bone, and changes in blood flow in the venous duct and tricuspid valve.[20] At US2T, between 20 and 24 weeks, these markers may be a fetal malformation, such as heart disease and duodenal stenosis; or a phenotypic sign, such as brachycephaly (anteroposterior flattening of the skull), shortening of the femur or medial curvature of the fifth finger of the hands (clinodactyly).[21,22]

After childbirth, in the neonatal period, the clinical signs include the following: hypotonia, muscle (you may notice, for example, that at the time of assuming the semi-fletid position, the child is in a batrachian position), brachycephaly, facial profile tv slots on the eyelid slanting to the top (on the outer corner of the eye, has a top elevation with respect to the "internal"), epicanthus (the fold of skin covering the inner corner of the eye, the ears small and dysplastic (abnormal development of the elements), short neck, with an excess of skin in the region of the nape of the neck, the protrusion of the tongue, the laxity of the joints of the hands are small, brachydactyly (short fingers), clinodactyly of the fifth finger of the hand, and the crease in transition palm, diastasis (separation) of the rectus muscle of the abdomen, and the increase of the distance between the 1st and 2nd toes.[9,23] In older children, other clinical features are significant, among them, short stature and delayed neuropsychomotor development.[9] Figure 2 shows some of the characteristics observed in the physical examination in people with DS.

Figure 2 – Features observed on physical examination in people with DS. 2A: thin and smooth hair, eyelid clefts oblique upwards, epicanthus, low nasal bridge, protruding tongue, short neck. 2B: small hands, brachydactyly, palmar transition fold. 2C: increased distance between 1st and 2nd pododactyls



Source: adapted from the GBDDC app. https://globalbirthdefects.tghn.org/download-birth-defects-surveillance-app/

Patients may also have other clinical findings such as congenital heart abnormalities, hypothyroidism, airway disorders, respiratory and hearing problems, autoimmune disorders, oncological and hematological complications, musculoskeletal changes (hip dislocation, atlantoaxial instability) and other neurodevelopmental disorders such as seizures and autism.[16]

DIAGNOSIS

At prenatal

There are a wide variety of screening approaches described for DS in the prenatal period. These include first trimester screening (assessment with us1t and serum markers); second trimester screening; and analysis of free fetal DNA in maternal blood.[24]

First trimester screening is usually performed between the 11th and 14th weeks of gestation and should include ultrasound evaluation with measurement of TN, evaluation of the nasal bone and venous duct.[25] In addition to the ultrasound examination, in some countries, the biochemical profile is performed during this period, with the dosage in maternal blood of free human β-chorionic gonadotropin (free β-hCG) and plasma protein A associated with pregnancy (PAPP-A).[26] The risk for chromosomal trisomies can be estimated from the results of tests performed in conjunction with other maternal factors, such as age and previous history of aneuploidy.[24,27] The risk must be calculated by specific algorithms, such as those of the Fetal Medicine Foundation (https://fetalmedicine.org/research/assess/trisomies), which considers as high risk the chance greater than 1:100 for fetal aneuploidy; intermediate risk between 1:100 and 1:1,000 and low risk less than 1:1,000.[28]

Regardless of the risk estimate after this screening, all pregnant women should perform US2T to evaluate structural abnormalities, since ultrasound markers can be identified. These markers have varying degrees of association with trisomy 21 and cannot be used in isolation to confirm or exclude the diagnosis.[24]

In 2011, the free fetal DNA screening technique (cfDNA) was introduced, which uses the analysis of cfDNA fragments in the maternal circulation, identifiable around the 9th-10th week of gestation and, unlike marker screening, can be performed until the end of gestation.[29] Screening for trisomies in single pregnancies by cfDNA in maternal blood has limitations, but it has high sensitivity to the main aneuploidies of autosomes (13, 18 and 21) and sex chromosomes (X and Y), being able to detect around 99% of fetuses with trisomy of 21, being superior to the other screening methods for DS, both in terms of detection capacity and lower false-positive rates.[24,30]

None of the tests described are diagnostic tests and patients with a positive screening test result for fetal aneuploidy should undergo genetic counseling and consider the possibility of Investigation with invasive confirmatory diagnostic tests in a fetal medicine service, such as chorionic villus biopsy, amniocentesis or cordocentesis for karyotype examination.[24] The use of invasive techniques for the diagnosis of DS in the prenatal period is indicated for pregnant women who have a relative risk, identified in the screening tests, greater than the risks associated with diagnostic methods, and the experience and skill of the doctor who performs the procedure are considerable factors in reducing the risk of fetal loss.[31]

In the postnatal period

After birth, recognition of clinical characteristics is essential for diagnosis. There are no defining criteria, but the more characteristics are recognized, the greater the safety for diagnostic definition. Chart 1 summarizes the main clinical signs of DS in the neonatal period according to the body segment and can be used as a guide for the physical examination of the newborn.

Chart 1 – Main clinical signs of Down syndrome in the neonatal period according to the body segment

	CLINICAL SIGNS
GENERAL	
Skin	Marbled curlew
Tonus	Hypotonia
SKULL AND FACE	
Aspect	Brachycephaly Thin, straight and sparse hair Low posterior hair implantation Short neck with leftover skin on the nape
Eyes	Oblique eyelid cleft Epicanthus Brushfield spots (white dots on the iris)
Ears	Low implanted small and/or dysplastic
Nose	Small low nasal bridge
Mouth	Protrusion of tongue
TRUNK	
Chest	Congenital heart abnormalities (most often defects of the atrioventricular and ventricular septum)
Abdominal wall	Diastasis of the rectus abdominis muscle umbilical hernia
LIMBS	
Upper	Brachydactyly 5th chirodactyl clinodactyly Small hands Transitional palmar fold
Lower	Increased distance between 1st and 2nd pododactyls Bending fold between 1st and 2nd pododactyls

Source: authors.

Although the diagnosis of Down syndrome after birth is mainly clinical, it is necessary to perform the karyotype examination to determine whether the cause is a structural change or an error due to non-disjunction, since this result is essential for determining the risk of recurrence and genetic counseling.[16,23]

In addition, diagnosis can be challenging in preterm infants, certain ethnic groups, and in some cases mosaicism.[16,23] In cases where the physical examination is not defining, the cytogenetic examination (karyotype) becomes fundamental for establishing the diagnosis.[9]

PREVENTION

For primary prevention of DS, the only known measure is conception at a younger maternal age, when this is possible. But there are several secondary and tertiary prevention measures such as follow-up from prenatal, surgical correction of associated congenital anomalies and early stimulation to enable better development.[23] This book has a specific chapter that presents in more detail the prevention of congenital anomalies.

GENETIC COUNSELING

In cases of DS by free trisomy of chromosome 21, the chance of recurrence should be estimated considering the influence of maternal age.[13]

When DS occurs due to unbalanced structural change in the karyotype, such as those caused by translocations, the risk of recurrence depends on whether one of the parents is a carrier of balanced translocation.[31] Thus, for genetic counseling of people with DS due to structural change, it is mandatory to conduct research with examination of the karyotype of the parents and maternal age has no influence on this etiology.[32,33]

FINAL CONSIDERATIONS

DS is the most common chromosomal change in humans and there are prevention measures and guidelines for Health follow-up of people with this condition.[9] Thus, security in the recognition of signs and symptoms allows not only better management of health problems associated with the syndrome, but also greater peace of mind in communicating with parents about the diagnosis or clinical suspicion.

During the prenatal period, in the care provided by the Unified Health System (SUS), for pregnancies considered as usual risk, an obstetric ultrasound is planned, preferably in the first trimester, with indication of referral to fetal medicine services if there are findings suggestive of genetic syndrome.[34] In the follow-up of high-risk pregnancies, invasive tests are indicated if there is a suspicion of DS.[35]

However, maternal blood tests for aneuploidy screening are not listed in the prenatal investigation routine in SUS, even for pregnant women older than 35 years.[34,35] CfDNA analysis is currently more advantageous in terms of technique for screening DS, being superior in sensitivity and specificity compared to other methods of serological screening, besides there is no risk of fetal loss.[29]

Study of the effectiveness in calculating the gestational risk for aneuploidies using the markers evaluated in the US1T (TN, nasal bone, venous duct and tricuspid regurgitation) in combination with maternal age for all pregnant women, followed by invasive diagnostic tests in the group considered high risk and cfDNA analysis for the treatment of aneuploidy. The intermediate risk pregnant women showed that this is a coherent approach, especially for cases of DS, with a detection rate of about 96%.[36]

It is known that about 130 million people – 62% of the Brazilian population – use the SUS as a health system and that, in 2013, around 74% of Brazilians did not have a health plan and private assistance reached only 5% of the poorest population.[37,38] Therefore, considering the incorporation of serological screening tests for chromosomal abnormalities by the SUS, depending on the risk detected by ultrasound, is a suitable measure for increasing suspicion in the prenatal period. The incorporation of cfDNA technology by the SUS, in reference services in high-risk fetal/gestation medicine, would allow more accurate screening in pregnant women with relative risk considered increased for aneuploidies after evaluation with US1T, being an option that deserves cost-benefit studies to determine criteria for its implementation in Brazil by the SUS.

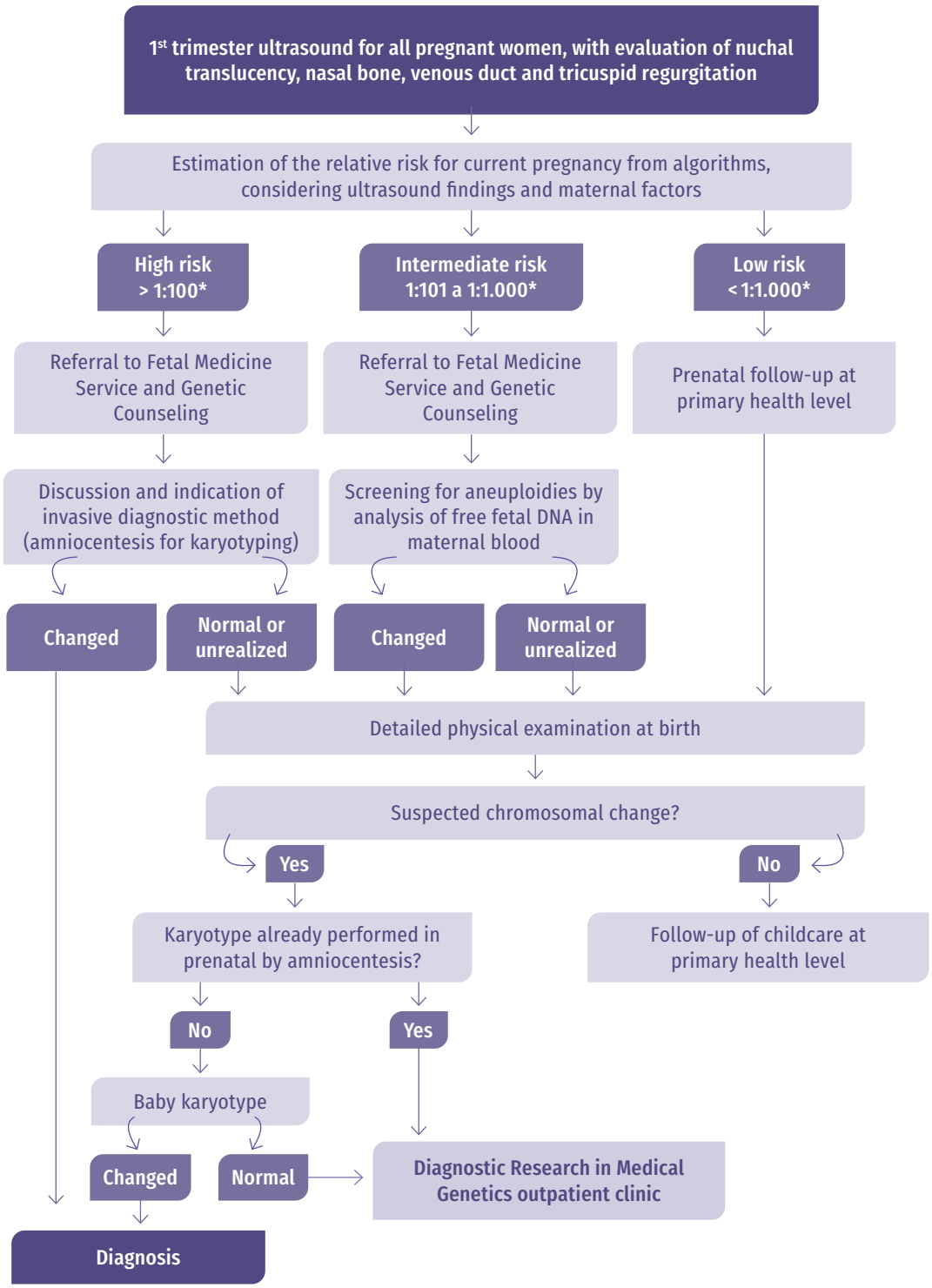
Evaluation with US2T can increase the diagnosis of fetal malformations and thus serve as an alert. For example, in cases of congenital heart malformations, the frequency of chromosomal abnormalities found can reach 23% (with an average of 9%, approximately 12 times more frequent than in people without heart disease), the most frequent being the free trisomy of chromosome 21.[39]

For surveillance after birth, training in the identification of signs characteristic of DS in the neonatal period is essential. It is necessary not only to know, but also to be familiar with the possible clinical signs and to know that the characteristics must always be evaluated together to establish the diagnosis.

In addition, the communication of the diagnosis or suspicion should be made in an appropriate manner and as early as possible and many parents report discontent with the moment when they received the news.[13,40] The training of teams of Pediatrics and obstetrics – usually the first to have contact with the baby – to recognize the characteristics, diagnose and talk with the family about DS safely and sensitively is essential.

Given the considerations, Figure 3 shows a flow chart with conducts that we propose for the operationalization of surveillance for DS in Brazil.

Figure 3 – Flow chart with the proposed conducts for the operationalization of surveillance for Down syndrome in Brazil



Source: authors.
Note: *Values considered as high, intermediate and low risk according to the *Fetal Medicine Foundation*.[28]

Actions planned to improve care for people with congenital anomalies in Latin America need government support and include the training of health professionals and the encouragement to seek care for patients to reduce complications.[41] In this sense, this narrative review aimed to discuss the aspects of DS and point out the main findings in prenatal and after birth to disseminate knowledge and propose measures to increase surveillance for this syndrome in Brazil.

HOW TO REGISTER?

DS, like the other CA treated in this book, must be registered in fields 6 and 41 from Live Birth Declaration. In field 41, not only DS, but also the presence of heart disease or another concomitant anomaly should be described.

ICDs for DS may vary according to cytogenetic change. However, the most common is to use the Q90 ICD.

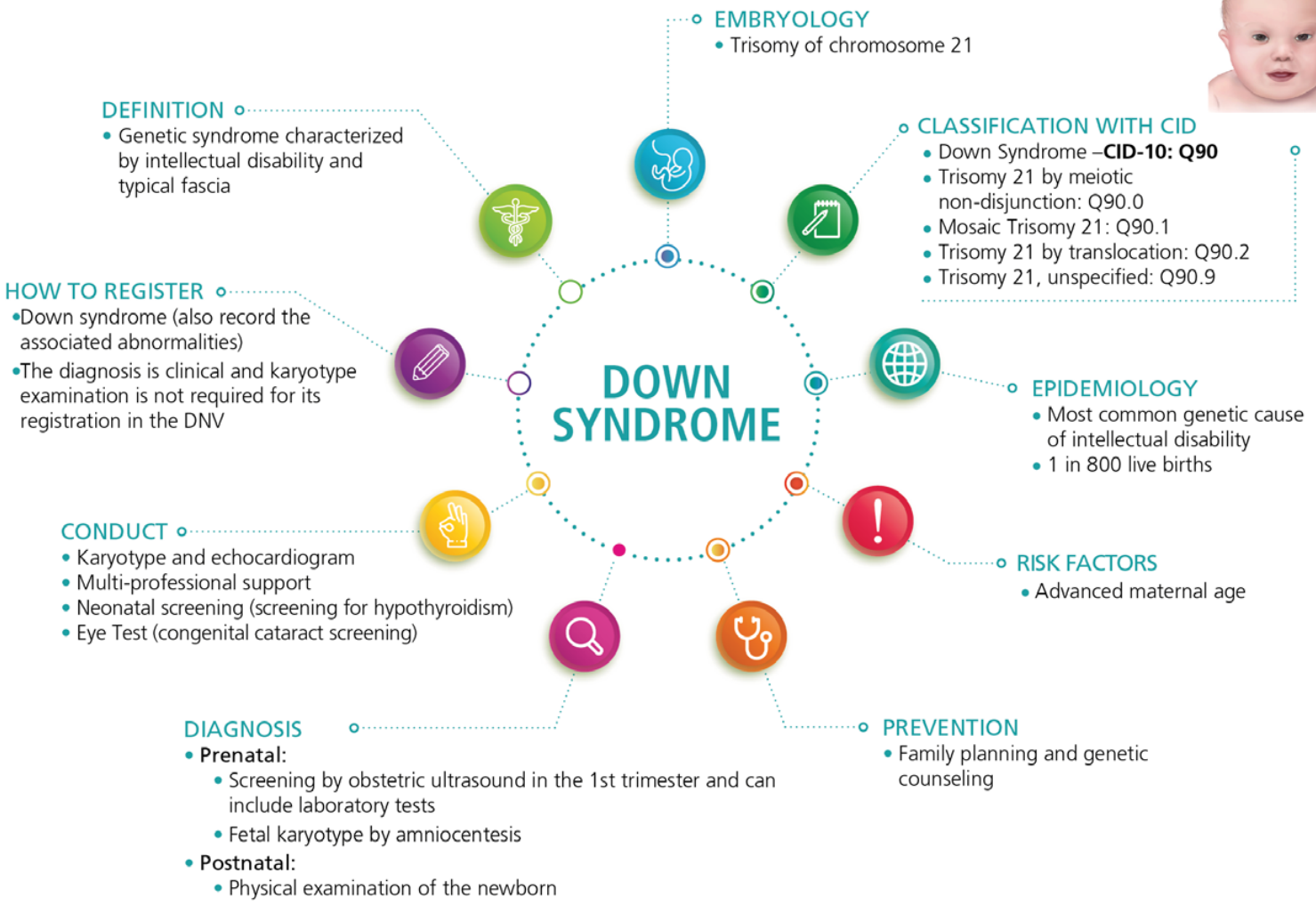
If other data are already available (karyotype result) can be used:

- Q90.0 Trisomy 21, not meiotic disjunction
- Q90.1 Trisomy 21, mosaicism (not mitotic disjunction)
- Q90.2 Trisomy 21, translocation
- Q90.9 Unspecified Down Syndrome

TO REMEMBER

- DS is not a rare condition and is the most common genetic cause of intellectual disability.
- Advanced maternal age is a known risk factor and increases the chance of a child with DS, but around 50% of children are born to mothers under the age of 35.
- There are examinations in the prenatal period that can lead to suspicion of the diagnosis even before birth. The physical examination of the newborn by experienced professional allows the clinical diagnosis after birth in most patients and the karyotype is not necessary for confirmation in these cases but is fundamental for genetic counseling.
- The Ministry of Health provides care guidelines for people with Down Syndrome in **https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_atencao_pessoa_síndrome_down.pdf**

INFOGRAPHIC



Source: authors. Infographic/images - WHO/CDC/ICBD. Original design Emphasis Design, Anomalias Congênitas/Surveillance RS, adapted from SVS.

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10 PREVENTION OF CONGENITAL ANOMALIES

SUMMARY

OBJECTIVE

To describe the state of the art on the prevention of congenital anomalies. This review offers a critical and personal analysis of the authors.

METHODS

Narrative revision of the literature, through search in the MEDLINE database (via PubMed), websites, reports and official documents.

RESULTS

For the prevention of CA, not only at the primary, but also secondary and tertiary levels, its proper registration is essential. Knowing the frequency, type and severity of anomalies and their distribution, provides a planning of strategies with different focuses, such as, for example, intensification of the vaccination program, preconception and prenatal education/guidance until the creation and implementation of reference centers. Avoiding alcohol consumption during pregnancy is an important measure of prevention of CA and intellectual disability. The control of maternal diseases is important in the primary and secondary prevention of CA.

CONCLUSION

Congenital anomalies are among the main causes of neonatal and infant mortality, chronic diseases and disability, having an impact on the individual, family, health system and society. In this sense, congenital anomalies are conditions of great relevance in the field of public health, and for the structuring of their effective prevention strategies, a strengthened epidemiological surveillance is necessary.

PALABRAS CLAVES

Primary prevention. Secondary prevention. Tertiary prevention. Congenital anomalies. Epidemiological surveillance.

INTRODUCTION

Congenital anomalies (CA) are among the main causes of neonatal and infant mortality, chronic diseases and disability, having an impact on the individual, family, health system and society. According to the World Health Organization (WHO), annually approximately 8 million newborns in the world are born with a serious defect or congenital anomaly and 3 million die before the age of 5. In Latin America, CA causes about 20% of deaths of children under 5 years of age and one in five babies dies of birth defects during the first 28 days of life.[1,2]

About 70% of CA can be avoided or its effects minimized with preventive actions, particularly in middle-income countries. Measures such as vaccination, food fortification and prenatal care can decrease the burden associated with many of these anomalies. The monitoring of geographical and temporal variations also contributes to the strategic planning of actions for public health. Prevention measures for CA require a range of strategies that include providing health care for women, newborns and children. In this sense, strategies that promote CA care and prevention are feasible, cost effective and should be a priority within public health policies.[1,3-5]

General recommendations for CA care and prevention can be focused on reducing risk, improving care, and empowering health professionals and civil society,[1,3-12] as follows.

RISK REDUCTION

- Educate the community, health professionals and workers, policymakers, the media and other stakeholders about CA and the opportunities for effective care and prevention.
- Promote family planning by allowing couples to decide when they want to have their children, organizing the interval between pregnancies, the number of children, the ages at which they want to complete families and reducing unwanted pregnancies.
- Ensure a healthy and balanced diet during the reproductive period through an adequate intake of macronutrients, a wide range of micronutrients and fortification when necessary. Special attention regarding the consumption of teratogenic substances such as alcohol intake.
- Optimize maternal health through the control of infectious and chronic diseases associated with an increased risk of CA.
- To train health professionals in the recognition of causes and care of children with CA.
- Perform physical examination of all newborns by health professionals trained for recognition before discharge from the hospital or clinic.
- Provide adequate child health services for the care of infants with CA.
- Establish surveillance and monitoring systems for common birth defects for robust evaluation of national and local interventions.
- Empower and support society on CA.

IMPROVEMENTS IN HEALTH SERVICES

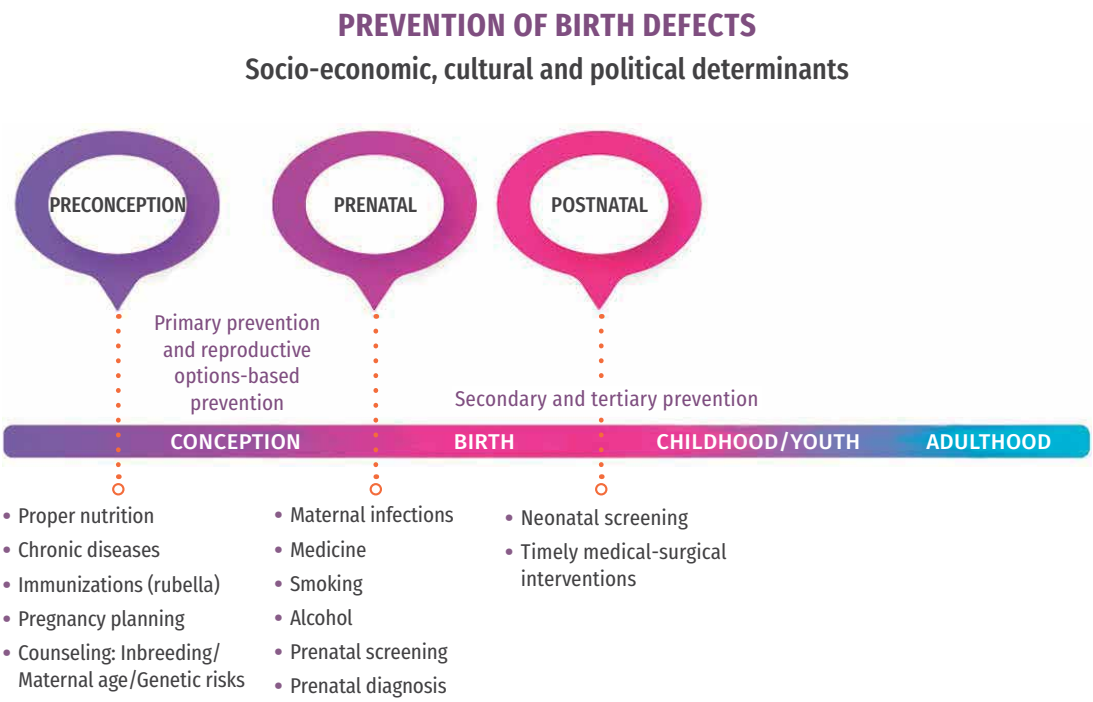
- Promote the training of health professionals who work directly or indirectly with CA in relation to the foundations and recognition of such anomalies, causes and care of children with CA and the guarantee of physical examinations of all newborns by trained health professionals before discharge.
- Ensure preconception medical services to help women and their partners achieve the optimal level of physical and mental health and well-being during pregnancy, as well as promote a normal and healthy delivery for the baby. These services should include genetic screening.
- Ensure effective services and treatments for CA, including surgery, medications, dietary modifications, and rehabilitation services when needed.
- Provide psychosocial support to families promoting a greater understanding of CA and managing the growth and development of children with CA.

EMPOWERING SOCIETY ABOUT CA

- Educate society about CA and how families can maximize the chances of a healthy pregnancy by monitoring health professionals.
- Strengthen ties of society through the promotion of support groups for patients and families and non-governmental organizations, with access to high-quality care family-centered patient quality, including facilitating community, professional awareness and education; and advocating for increased funding for research on the causes of congenital diseases.
- Train health professionals in relation to the fundamentals of medical genetics. This training should include the diagnosis of common congenital diseases before and at birth; treatment, where possible, in the primary health care environment; recognition of the need for referral to specialized treatment; basic genetic counseling, including best practices in communicating health information to parents and support for families who have a child or are at increased risk of having a child with a congenital disease. Genetic counseling aims to empower those who are advised to make autonomous decisions regarding their health according to their religious and ethical beliefs.
- Establish health services to assist families in achieving optimal physical and mental health and well-being and to facilitate a healthy pregnancy and childbirth. These services include rubella immunization; screening for the risk of genetic, partially genetic and teratogenic congenital diseases, and mental health counseling, including identification and support for depression.
- Implement preconception or prenatal medical screening to identify families at risk of having a baby with hemoglobin disorders; Down syndrome; blood type incompatibility; sexually transmitted congenital infections such as syphilis, human immunodeficiency virus and herpes simplex virus and structural malformations, particularly neural tube defects.
- Avoiding exposure to risk factors, seeking early diagnosis and adequate care, minimizing complications should be a constant part of government strategic planning.

CA prevention can occur at three levels of attention. Primary prevention is preconception and prevents the occurrence of the anomaly; secondary is prenatal and prevents the birth of an embryo or fetus with CA; tertiary is postnatal and prevents complications arising from CA, providing better quality of life. Figure 1 also shows the important steps in the different moments of life for the prevention of CA.

Figure 1 – Opportunities and actions, throughout life, for the prevention of congenital anomalies



Source: authors.

PRIMARY PREVENTION

Primary prevention of many birth defects is feasible, as many of the risk factors are well established. Strategies to avoid them go through community-oriented educational programs such as awareness of the use of medications only with their proper prescription and treatment of chronic diseases for women of childbearing age. Scientific research is important because it allows to identify new risk factors or new aspects of already known factors. Constant education about the harms of alcohol and tobacco is essential (Chart 1).

Chart 1 – Primary prevention strategies for congenital morphological anomalies and embryo/fetal losses

STRATEGY	CONGENITAL ANOMALY	REFERENCES
Supplementation with periconceptional folic acid, preferably weeks before	• Neural tube closure defects • Cardiac abnormalities • Abnormalities of the urogenital system Cleft lip • Anomalies of lower limbs	7,18-22
Avoid alcohol intake	• Fetal alcohol syndrome • Diaphragmatic hernia • Gastroschisis • Neural tube closure defect	7,9,18,21,23
Smoking cessation and other drugs	• Cleft lip • Neural tube closure defect • Cardiac abnormalities • Intrauterine growth restriction • Gastroschisis • Anomalies of lower limbs	7,9,10,18,19,21
Prevent obesity and associated metabolic disorders changes	• Neural tube closure defect • Cardiac abnormalities	7,10,21
Vaccination and behavioral measures aimed at preventing exposure to pathogens (correct cleaning of food, correct washing of hands, not sharing objects with people possibly contaminated, among others)	It depends on the pathogen and the time when exposure occurred: • Fetal death and abortion • Microcephaly and other changes in the central nervous system • Eye abnormality • Heart abnormalities • Craniocerebral abnormalities	7–10,21,24,25

To be continue

Conclusion

STRATEGY	CONGENITAL ANOMALY	REFERENCES
Tracking and proper treatment of women of childbearing age with chronic diseases (diabetes *mellitus*, hypertension, hypothyroidism)	• Intrauterine growth restriction • Central nervous system anomalies • Other congenital anomalies	7,9,10,18,21
Avoid exposure to environmental pollutants	• Cardiac abnormalities • Neural tube closure defect and other central nervous system changes • Cleft lip • Hypospadias • Abnormalities of the respiratory tree • Abnormalities of the urogenital system • Abnormalities of the gastrointestinal system • Abnormalities of the musculoskeletal system • Hemangioma and lymphangioma • Chromosomal abnormalities • Fetal death and abortion	7,9,10,18,21

Source: authors.

SECONDARY PREVENTION

Secondary prevention of morphological congenital anomalies is still very restricted, since most congenital anomalies do not have a treatment that completely avoids sequelae. Intrauterine surgeries of neural tube closure defects (myelomeningocele) are already a reality and show promising ways of secondary prevention of the problems associated with this anomaly. Similarly, early diagnosis of some congenital heart defects allows effective surgical interventions.

An important group of anomalies that do not involve morphological changes can be detected by specific tests. The National Neonatal Screening Program (PNTN) is a successful example of secondary prevention of a number of disabilities, but that escapes the scope of this chapter, which is aimed at morphological anomalies. But even in the PNTN, the heart test (*teste do coraçãozinho*) is able to identify severe congenital heart abnormalities amenable to effective surgical intervention.

Prenatal diagnosis followed by termination of pregnancy of fetuses with congenital anomalies is considered as one of the modalities of secondary prevention. In Brazil, legally only anencephaly is included in this category.

TERTIARY PREVENTION

Tertiary prevention occurs in the postnatal period and aims to rehabilitate, re-socialize and avoid complications arising, in this case, from CA, with the aim of improving not only survival but also the quality of life of affected children. It involves medical attention, available technology, early detection and multi-professional care, according to the needs of each individual, without forgetting the psychological well-being of the family. Chart 2 provides some examples of tertiary prevention for some of the anomalies addressed in this volume. It is important to emphasize, once again, that early diagnosis of CA and adequate registration will allow timely referral to this type of prevention, allowing the organization of the care network, contributing to better results.

Chart 2 – Examples of tertiary prevention for congenital anomalies

TYPE OF ANOMALY	TYPE OF PREVENTION	REASON
Oral clefts	Periodic otorhinolaryngological evaluation	Fluid retention in the middle ear and hearing loss
	Orthodontic treatment	Absence of some teeth or misalignment
Down Syndrome	Periodic hormonal dosage	Altered functioning of the thyroid gland
	Early stimulation	Development Delay
Neural tube closure defects	Hydrocephalus	Accumulation of fluid in the ventricles
	Self-catalyzing and/or medicinal products	Urinary incontinence

Source: authors.

BIRTH DEFECTS SURVEILLANCE RECORDS

In recent years, a significant number of CA surveillance systems/programs have been developed, particularly after the tragedy of thalidomide use in the 1960s. These programs have as main objective to monitor and diagnose CA in order to implement prevention and treatment strategies as early as possible.[3,13]

Overall, surveillance systems can be classified as population-based or hospital-based. Population-based systems investigate CA from birth in the population residing in a specific area. On the other hand, hospital-based patients diagnose cases of CA in hospitals, maternity hospitals or certain places whose coverage corresponds to the births that occurred in these places. Within hospital-based surveillance, there is also sentinel surveillance, usually deployed in specific places in order to obtain more agile assessments of the occurrence of a gestational outcome. Systems can contemplate surveillance in a restricted area within a country, across the country, or contemplate data from different countries.[3,7,14-16]

A narrative review, published recently, have identified six networks of international collaboration for the surveillance of congenital abnormalities: the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR); the European Surveillance of Congenital Anomalies (EUROCAT); the British and Irish Network of Congenital Anomaly Researchers (BINOCAR); Red Latinoamericana de Malformations Congenital (ReLAMC); South-East Asia, Region's Newborn, and Birth Defects of the Database (SEAR-NBBD) and in Studio as a Collaborative Perception of Malformations Congenital (Eclamc). These networks include 98 programs present in 58 different countries on all continents except Africa. These networks have different characteristics, but all have as a common goal to promote CA surveillance.[3]

Brazil is a historical member of the Eclamc network (http://www.eclamc.org/port/index.php).[7,17] Eclamc is a program in which the main objective is to conduct clinical and epidemiological research of risk factors for CA in Latin American centers. This program uses a case-control methodology, that is: each newborn with CA (case) is paired with the next born without malformations, of the same sex and in the same hospital (control). Eclamc covers 12 countries in Latin America. Eclamc was the first network created and the longevity of the records allows this network to formulate temporal trends for the frequency of CA, which has been contributing to advances in the area of CA. Another strength of this network is the egalitarian and voluntary model of this organization. This means that hospitals are not required to report the data periodically and the health professionals involved are considered researchers and co-directors of the program, with equal access to the data collected. In this sense, Eclamc promotes research related to CA, provides primary and secondary prevention manuals and offers an online tool (Congenital Malformations Browser) that associates the name of the change or the code of the tenth revision of the International Statistical Classification of Diseases and Health-Related Problems (ICD-10) with images of the most common malformations.[3]

The ReLAMC network was created in 2016 in the post-epidemic context of microcephaly linked to congenital infection by the Zika virus in northeastern Brazil. ReLAMC aims to provide updated epidemiological data on CA derived from Latin American hospital and population records of participating countries. The network includes ten sources of records, five of which have national coverage, four subnational and one multinational-Eclamc. It is noteworthy that ReLAMC extrapolates the purposes of Eclamc by including Population Database records.[3,16]

HOW TO REGISTER?

For live newborns, it is important to register in the Live Birth Declaration , starting with field 6 of block I. In this place, it should be marked YES if the child presents any type of anomaly, regardless of whether it is greater or lesser. Next, in field 41 of block VI, all anomalies present must be described, without hierarchy or attempt to group them into syndromes. The qualified coding of the described anomalies should preferably be carried out in a second moment by people trained for this function. Therefore, the better the anomaly described, the better the coding work will be.

TO REMEMBER

- For the prevention of CA, not only at the primary, but also secondary and tertiary levels, its proper registration is essential.
- Knowing the frequency, type and severity of anomalies and their distribution, provides a planning of strategies with different focuses, such as, for example, intensification of the vaccination program, pre-conception and prenatal education/guidance until the creation and implementation of reference centers.
- Avoiding alcohol consumption during pregnancy is an important measure of prevention of CA and intellectual disability.
- The control of maternal diseases is important in the primary and secondary prevention of CA.

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PART II

EXPERIENCE REPORTS AND TOOLS FOR EPIDEMIOLOGICAL SURVEILLANCE

11

FROM THE PUBLIC HEALTH EMERGENCY DUE TO THE INCREASE IN THE OCCURRENCE OF MICROCEPHALY TO THE SURVEILLANCE OF CONGENITAL ANOMALIES: THE EXPERIENCE OF THE BRAZILIAN MINISTRY OF HEALTH

SUMMARY

OBJECTIVE

To report the experience of the response to the Emergency in Public Health of National Importance (Espin) by the change in the pattern of occurrence of microcephaly in Brazil, from the perspective of the Ministry of Health (MoH), as well as its history and continued actions in the post-emergency period.

METHODS

To base the discussion, an analysis of the official documents published by the MoH from 2015 to 2020 was carried out, including legal regulations, protocols, epidemiological bulletins and other publications. To characterize the prevalence of congenital anomalies (CA) of the brain, eye and microcephaly at birth, in the pre, during and post-emergency periods, Sinasc records were analyzed between 2000 and 2019. Live Births (LBs) confirmed with Congenital Zika Syndrome (CZS), during and post-emergency period (2015 to 2019), were analyzed from the Public Health Event Registry (Resp-microcephaly).

RESULTS

The actions carried out and the strategies adopted by the MoH in the response to Espin were presented, as well as the continuity of actions in the post-emergency period. Between 2000 and 2014, the prevalence of microcephaly at birth showed some stability, with an annual average of 164 cases registered in Sinasc. In 2015, the prevalence of microcephaly at birth was 5.83 cases per 10 thousand LBs, being even higher in 2016, with 7.96 cases per 10 thousand LBs. There was an increase in the number of cases of CZS from August 2015, reaching a peak in December (437 LBs with CZS). A second wave was observed in the second half of 2016. Between 2017 and 2019, the number of cases decreased again, however new cases of CZS continue to occur in the country.

DISCUSSION

In the post-emergency period, it became clear the need to keep active the surveillance of the new cases of CZS that continue to emerge in the country, in addition to the urgency to implement a national program of surveillance of congenital anomalies.

KEYWORDS

Zika virus infection. Microcephaly. Emergency. Public health. Surveillance in public health.

INTRODUCTION

Microcephaly is a congenital anomaly that usually reflects not only in the size of the brain, but also in the changes of brain structures, being common children with microcephaly present cognitive and motor impairment.[1,2] In this sense, the monitoring of cases of microcephaly at birth is essential for the recognition of the existence and increase of risk factors, as well as for the better design of actions aimed at the health care of individuals with this condition.

Microcephaly is defined from the measure of head circumference, using as a cut-off point less than two standard deviations below the mean for the same age and sex, in relation to a reference standard.[1,3] When the measurement is below three standard deviations from the mean, microcephaly is considered severe.[1] For the diagnosis of microcephaly, it is recommended that the measurement of the head circumference be made in the delivery room at the time of birth and repeated after 24 hours.[4] The values obtained should be recorded in cranial growth charts, which allow comparison with the reference values and monitoring of the growth curve for the child.[4]

Etiological factors of microcephaly can be genetic, environmental or even multifactorial. Genetic causes include chromosomal abnormalities and genetic changes. Environmental causes can be: maternal infections during pregnancy, including syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes (STORCH); maternal diseases and conditions, such as uncontrolled diabetes, malnutrition, among others; and exposure to teratogenic substances, such as alcohol, radiation, among others. The combination of different genetic or environmental factors configures a multifactorial etiology.[5,6]

In 2016, the Zika virus (ZIKV) was recognized by the World Health Organization (WHO) as a human teratogen.[7] The congenital changes caused by ZIKV, which include microcephaly, intracranial calcifications, brain atrophy, among others, began to compose a phenotypic picture called congenital Zika syndrome (CZS).[8]

In Brazil, the first suspected cases of ZIKV infection were reported in October 2014, in the state of Rio Grande do Norte, as an outbreak of rash of unknown origin.[9] On April 29, 2015, ZIKV was first identified in cases in the state of Bahia.[10] Concomitant with its confirmation, an increase in the number of hospitalizations for neurological manifestations was observed in the country.[11]

In October 2015, clinical reports indicated an increase in the number of babies with microcephaly at birth in northeastern Brazil, where ZIKV was circulating.[12] At the time, a possible association between these two events was suggested. Several studies began to investigate the possible association between ZIKV and the occurrence of microcephaly, as well as other congenital anomalies. Initially, it was shown that ZIKV was able to cross the placental and blood-brain barrier, infecting developing embryos or fetuses and, in many cases, causing a series of anomalies or pregnancy loss.[13] The detection of the virus, its genetic material and antigens, in the brain tissues of cases with congenital ZIKV infection and in placental tissues of early abortions, provided more robust evidence of the association between ZIKV infection and cases of microcephaly.[13-15]

Finally, very particular characteristics of microcephaly showed a different syndromic pattern than previously associated with this congenital anomaly, suggesting an infectious etiological agent and previously nonexistent in our environment.[16]

In this context, this chapter aimed to report the experience of the response to the Emergency in Public Health of National Importance (Espin) by the change in the pattern of occurrence of microcephaly in Brazil, from the perspective of the MoH, as well as its history and continued actions in the post-emergency period.

METHODS

An analysis of the official documents published by the MoH in the period from 2015 to 2020 was carried out, including legal regulations, protocols, epidemiological bulletins and other publications. The legal framework for the Declaration of Espin for changes in the pattern of occurrence of microcephaly in Brazil was Ordinance No. 1,813 of November 11, 2015. This was the first Espin declared in Brazil since 2011, when this modality was regulated under the federal government. Officially, Espin was closed on July 30, 2017, with the publication of Ordinance No. 1.682. The main events preceding the Declaration of Espin (pre-emergency period), the response to Espin between November 2015 and July 2017 (emergency period), and the continuity of actions within the MoH in the post-emergency period (2017 to 2020) were described.

To characterize the occurrence of congenital anomalies in Brazil in the pre-emergency period, data from the Live Birth Information System (Sinasc) were used. The records were selected from the physician's description, in the Live Birth Declaration (DNV, in Portuguese), of the congenital anomalies identified at the time of birth. The anomalies were later codified using the 10th revision of the International Statistical Classification of Diseases and Health-Related Problems (ICD-10). Records with reference to codes Q00-Q07 and Q10-Q15 were selected to estimate the prevalence at birth of congenital anomalies of the brain and eye, respectively, possibly associated with congenital ZIKV infection, as proposed by Passion et al.[17] To estimate the prevalence of microcephaly at birth, records with reference to the code Q02 were selected. The public bases of Sinasc were used, made available by the MoH at the link: **https://bit.ly/3b3ZLQc**.

To describe the prevalence of CZS in Brazil, during and post-emergency periods (2015 to 2019), data from the Public Health Event Registry (Resp-Microcephaly) were analyzed. The prevalence was calculated using as denominator all live births registered in Sinasc, in the period studied, for 10 thousand. For the analysis, R Studio, Tabwin and Excel software were used.

RESULTS AND DISCUSSION

The alert

The State Health Department of Pernambuco (SES/PE) detected an unexpected increase in newborns with microcephaly in the state[11] and notified the Secretariat of Health Surveillance (SVS) of the MoH on **October 22, 2015**. The unprecedented change in the pattern of occurrence of microcephaly in newborns and its serious impact on Public Health met the criteria of the International Health Regulation (RSI-2005)[11], which led the MoH to notify the WHO of the event on **October 23, 2015**.

Soon after, field investigations were started, which counted on the participation of the Training Program in Epidemiology applied to the services of the Unified Health System (EpiSUS). The microcephaly patterns of newborns were compatible with outcomes of a congenital infection; in addition, there were reports of cases of exanthemas in the mothers of these children during gestation. This episode suggested a possible relationship between the increase in microcephaly cases and the occurrence of ZIKV in Pernambuco.[18]

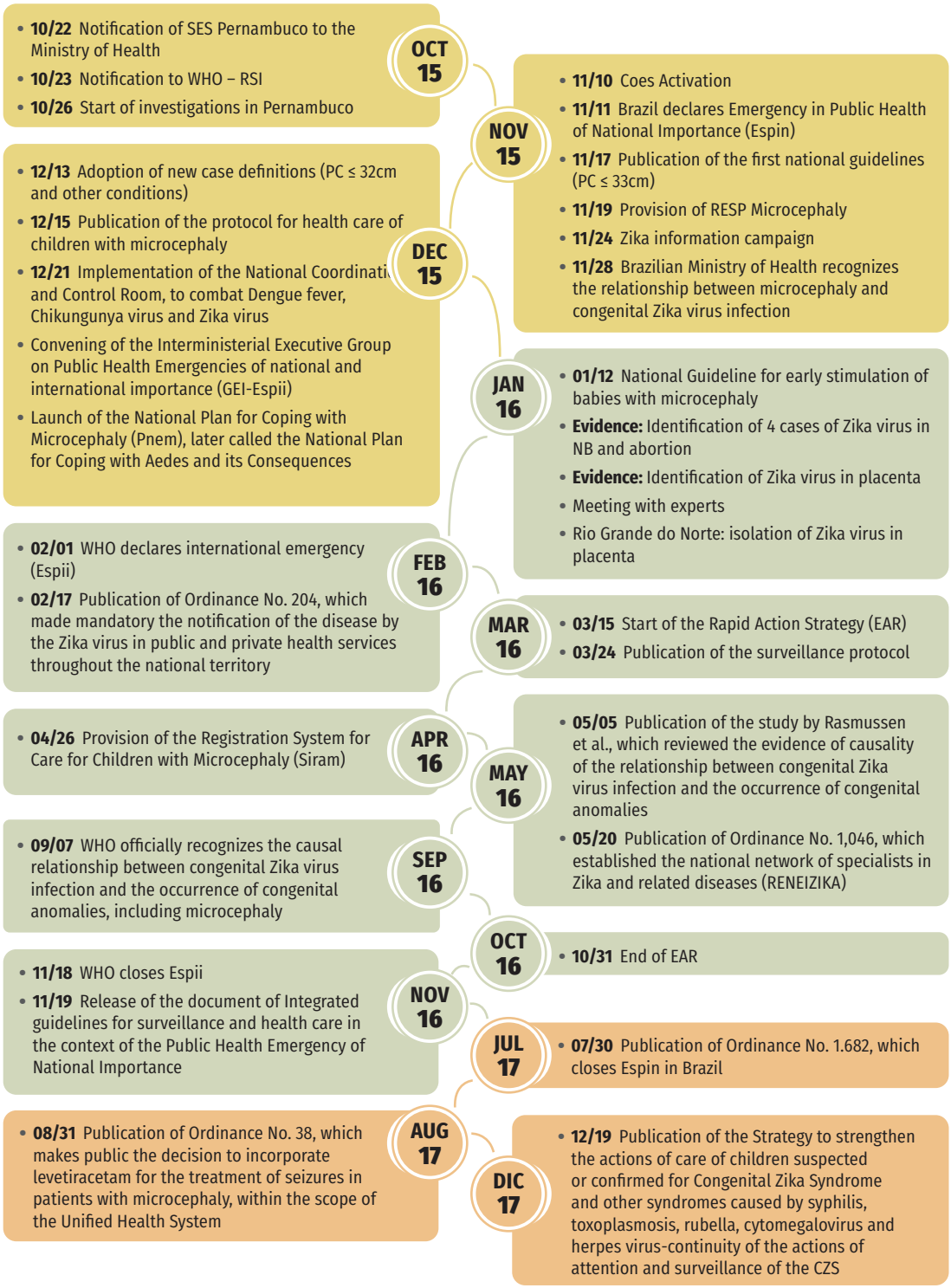
Reports of an increase in the number of microcephaly cases also began to be observed in other states of Brazil. On **November 10, 2015**, the Health Emergency Operations Center (Coes) was established, under the management of the SVS and with the participation of managers from different sectors of the MoH, as well as specialists in several areas. Coes aims to promote coordinated response through articulation and integration of the actors involved. Its structuring allows the analysis of data and information to support the decision-making of managers and technicians, in the definition of appropriate and timely strategies and actions for coping with public health emergencies.[19]

At the first Coes meeting, held on **November 10, 2015**, the managers of the MoH, in collaboration with experts from various areas, recommended the Espin declaration. Thus, on **November 11, 2015**, was published at the Ordinance No. 1.813, which declared Espin in Brazil and officially established the Emergency Operations Center (COE) as a mechanism for coordinated national management of emergency response at the national level.

The response to the national emergency

Figure 1 presents a timeline with the main events related to the emergency response, in Brazil and in an international context.

Figure 1 – Timeline of events related to the public health emergency by the change in the pattern of occurrence of microcephaly in Brazil, 2015-2017



Source: authors.

In **November 17, 2015** the first national guidelines for surveillance were published, adopting as a definition of microcephaly case the head circumference ≤ 33 cm, for both sexes, considering the measurement at birth. It was decided at that time to adopt a more sensitive case definition for surveillance, different from the international definition of microcephaly, in order to allow a greater capture of suspected cases.[36] With the evolution of knowledge, this definition has undergone changes over time, becoming increasingly specific (Chart 1). The first definitions adopted the same cut-off point for both sexes, which led to a higher uptake of female cases, since girls tend to have a head circumference, on average, smaller than that of boys, but within the norm. This finding led to the adoption of a gender-specific cut-off point, considering the international standards of the WHO and the Intergrowth 21st study.[20,21]

Chart 1 – Case definitions for microcephaly at birth adopted over time

PERIOD	CUT-OFF POINT FOR TERM NEWBORNS	CUT-OFF POINT FOR PRE-TERM NEWBORNS
November 17 to December 12, 2015	≤ 33cm for both sexes	≤ 3rd percentile of Fenton[22] by gestational age and sex
December 13, 2015 to March 12, 2016	≤ 32cm for both sexes	≤ 3rd percentile of Fenton[22] by gestational age and sex
March 13, 2016 to the present	<-2 standard deviations (WHO standards)[20] (<31.5 cm for girls and 31.9 cm for boys)	<-2 standard deviations from the Intergrowth reference[21] by gestational age and sex

Source: Adapted from França *et al.*[37]

On **November 19, 2015**, an electronic form was made available by the MoH to register suspected cases of microcephaly, called Resp-microcephaly.[23] The form recommended the integrated monitoring of surveillance and health care of conditions related to infections during pregnancy, identified in prenatal, childbirth and childcare. Because it is an open form, any health professional could report a suspected case of microcephaly directly to the Resp-Microcephaly. These records were subsequently evaluated by the surveillance teams, who were responsible for the investigation, classification and conclusion of these cases.

With the implementation of the national Coes and the establishment of the Resp, surveillance processes were built and disseminated to the emergency alert and Response Network formed by the Strategic Health Surveillance Information Centers (Cievs), present in all states and capitals of the Country.

On **November 28, 2015**, the MoH recognized the association between congenital ZIKV infection and the occurrence of microcephaly and other changes in the central nervous system. The MoH had been informed, by the Evandro Chagas Institute, about the identification of ZIKV in blood and tissue samples of a baby with microcephaly and other congenital anomalies, born in the state of Ceará. Brazil was a pioneer in recognizing this relationship, based on information from the national epidemiological surveillance and the identification of ZIKV in samples of infants with abnormalities.[24,25]

On **December 15, 2015**, the Ministry of Health published the first version of a document with guidelines targeting women of childbearing age, pregnant and postpartum women and newborns with microcephaly, entitled *Health Care Protocol and Response to the Occurrence of Microcephaly Related to Zika Virus Infection*, organized by the Secretariat of Health Care (SAS) with the support of specialists.[26] The objective of this document was to support professionals and managers of the Unified Health System (SUS) in the organization of its care network for care actions, whether for prevention, treatment or rehabilitation.

Also in December 2015, the National Plan for Coping with Microcephaly (Pnem) was prepared, later called the National Plan for Coping with Microcephaly. *Aedes* and its Consequences. Within the framework of the federal government, the actions were organized in three axes: mobilization and *Aedes aegypti*; care to the affected individuals; and technological development, education and research. Each of the axes provided for several actions, including support for the development of these at local and regional level.

To assist in the fight against *Aedes*, the National Coordination and Control Room was established for the fight against dengue, chikungunya virus and ZIKV, through Decree No. 8.612, of **December 21, 2015**. In addition, State and Municipal Rooms were implemented for control and combat actions, integrating several sectors. In the axis of care, the actions developed sought to offer actions and health services that assist in diagnosis and also in comprehensive care and rehabilitation. In the context of social assistance, social assistance services were mobilized to support families and accelerated the process with the social security services to grant benefits. More than 2,500 families had access to the Continued Cash Benefit during this period.

On **January 12, 2016**, a document with the *Early Stimulation Guidelines: children from zero to 3 years with neuropsychomotor development delay*, which updated the care guidelines for newborns with neurological changes resulting from ZIKV, such as visual and auditory changes, to support health professionals who work especially with rehabilitation. The guide was also published Caring for Developing Children, aimed at families and caregivers of babies, addressing simple practices of care and stimulation that could be applied at home, in the day to day, such as massages and orofacial stimuli for breastfeeding.

On **February 1, 2016**, WHO stated that the clusters cases of microcephaly and neurological changes in areas with ZIKV transmission constituted a Public Health Emergency of International Importance (Espii). Based on the available evidence, WHO stressed the importance of taking forceful measures to reduce the spread of ZIKV, especially among pregnant women and women of reproductive age. In addition, it stimulated the intensification of research initiatives aimed at the development of diagnostic techniques, vaccines and treatments.[27]

Still on **February 1, 2016**, the federal government published Decree No. 8.662, which dealt with the adoption of routine measures to prevent and eliminate mosquito outbreaks *Aedes aegypti*, within the framework of the bodies and entities of the Federal Executive Power, creating the Committee for Articulation and Monitoring of mobilization actions for the prevention and elimination of mosquito foci.

On **February 17, 2016**, Ordinance No. 204 was published, which redefined the National List of Compulsory Notification of diseases, illnesses and public health events in public and private health services throughout the national territory. Through this ordinance, the weekly notification of cases of acute disease by ZIKV became mandatory, as well as the immediate notification, within 24 hours, of acute disease by ZIKV in pregnant women and any death with suspected disease by ZIKV.

The Rapid Action Strategy began on **March 15, 2016**, as a joint action between health and social assistance that sought to clarify the diagnosis and refer, in a timely manner, families to access the Continued Cash Benefit (CPB), which helped in family income, contributing even in access to health services. The main objective at that time was to help local systems to carry out diagnoses more quickly, including several specialties and support examinations. On this occasion, several "campaigns" were organized throughout the country. The strategy lasted until October 31, and 6,694 cases were clarified through this initiative.

Within the framework of the Coes actions, technical discussions were held between various areas of the MoH and experts from various sectors, together with representatives of the State and Municipal Health Departments for the construction of the *Surveillance Protocol and Response to the Occurrence of Microcephaly and/or Changes in the Central Nervous System (CNS)*. The first version of the document was officially released on March 24, 2016, containing general information, technical guidelines and guidelines related to the surveillance actions of microcephaly and/or changes in the central nervous system suggestive of congenital infection throughout the national territory.

On **April 26, 2016**, the MoH made available the System of Registration of Care for Children with Microcephaly (Siram). The system was developed to record the follow-up of care to children with suspected or confirmed microcephaly, regardless of the association with ZIKV infection. The platform was made available to managers of public and private health networks in order to follow the trajectory of care for each child in the health system.

On **May 19, 2016**, it was published a study that reviewed the causality of the association between congenital ZIKV infection and the occurrence of congenital anomalies in the fetus.[28] This recognition highlighted the understanding that microcephaly is a clinical sign that reflects a disorganization in the formation of the brain and that may result in the delay in the development of children, in need of follow-up and care for a long period. In the most severe cases, it is accompanied by a number of other neurological manifestations similar to cerebral palsy. The observation of imaging tests and brain necropsy with characteristic changes led to the identification of CZS. This situation warned about the need to monitor the congenital anomalies resulting from ZIKV infection and the most frequent intrauterine infections that make up the acronym STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex).

The national network of specialists in Zika and Related Diseases (Renezika) was established by Ordinance No. 1,046 of May 20, 2016, involving more than 200 members, from 21 institutions in 4 countries (Brazil, Canada, USA and England). The objective of Renezika was to gather the best expertise of researchers in networks to articulate knowledge and discoveries, enhancing

the construction of rapid responses to the challenges of the emergency. The importance of the articulated work that was sought to develop, between health system management and researchers, is highlighted. In response to a public health emergency, in which very little is known about the natural history of the disease, and a coordinated work between managers, researchers, and health-care workers is essential, it speeds up the process of observation, analysis, and production of knowledge, as well as it also helps in the rapid incorporation of new therapeutic interventions and surveillance in public health.

On **June 27, 2016**, Law No. 13,301 was published with provisions on the adoption of health surveillance measures when verified a situation of imminent danger to public health by the presence of the mosquito transmitting dengue virus, chikungunya virus and Zika virus; and amended Law No. 6,437, of August 20, 1977. Through this law, a series of activities focused on prevention and combating the vector was made possible.

On **July 7, 2016**, Law No. 13,310 opened extraordinary credit, in favor of the Ministries of Science, Technology and Innovation, Defense and Social Development and combating hunger, in the amount of 420 million reais, for the development of various actions, and part of this resource was used for the acquisition and distribution of repellents for pregnant members of families beneficiaries of the Bolsa Família Program (PBF), aiming to reduce the risks *Aedes aegypti* and the occurrence of microcephaly in unborn children.

WHO has only officially recognized the causal relationship between ZIKV infection during pregnancy and the occurrence of congenital anomalies, including microcephaly, on **September 7, 2016**.[7] The statement was based on a systematic review of the literature, conducted by the WHO Zika Causality Working Group, which found 72 studies that directly addressed the relationship between ZIKV and the occurrence of congenital anomalies.[29]

Espii was officially closed by WHO on November 18, 2016.[30] The following day, the Brazilian Ministry of Health released the preliminary version of the document *Integrated Health Surveillance and care guidelines in the context of the Public Health Emergency of National Importance*, first protocol built jointly between the areas of surveillance and health care. The document reinforced the Brazilian commitment to the continuity of actions aimed at prevention, surveillance and health care of children. Guidelines aimed at monitoring changes in growth and development, identified from gestation to early childhood, related to congenital infections caused by various agents, called under the new acronym STORCH-Z (STORCH + Zika) were included. Despite the official closure of Espin on **July 30, 2017**, with the publication of Ordinance No. 1,682, the integrated guidelines document continued to be used by surveillance and health care teams, guiding actions in the post-emergency period.

Another important initiative was the publication of the *Apoio Psicossocial a Mulheres Gestantes, Famílias e Cuidadores de Crianças com Síndrome Congênita por Vírus Zika e Outras Deficiências: guia de práticas para profissionais e equipes de saúde*. This work was a cultural adaptation of a material produced by the WHO in order to support the families in the different stages of the process of gestating, giving birth, caring and seeing the growth of a child with CZS.

In the Renezika agenda with experts, at the beginning of 2017, for work on the theme of health care, it was agreed on the need for advances in actions and policies related to congenital anomalies, seeking to build a proposal for surveillance and care for children with congenital anomalies, at first, focusing efforts on infectious causes, and that the SUS could induce preventive actions of faster impact to, later, advance in actions to raise awareness also on the other causes.

Following the actions, to support SUS professionals and managers, the Ministry of Health promoted different educational initiatives and offers. For example, the Design of the Training of Professionals for the Early Stimulation in Children with Microcephaly, which was developed in partnership with the Hospital do Coração (Hcor), by means of the Program is to Support the Institutional Development of the Unified Health System (Proadi-SUS), had the goal of building the capacity of professionals to the top level of the primary care and specialized services for the care of the child with microcephaly, through the development of skills in the multidisciplinary team for evaluation and development in children from zero to 3 years, the management, and the techniques for early stimulation; and management, and guidance to family members and caregivers. Face-to-face practical workshops were held in six FUs in the Northeast (Ceará, Bahia, Rio Grande do Norte, Piauí, Paraíba, Maranhão) and one in the Midwest (Mato Grosso), and a total of 435 professionals completed the training. Another action carried out through this project was the elaboration and printing of 10 thousand copies of the *Manual do Multiplicador das Oficinas Presenciais* for distribution to all FUs.

For the development of technologies for diagnosis, treatment, vaccines and vector control, the MoH has carried out a series of actions and project support since the beginning of Espin, as highlighted below:

- Hiring of approximately 150 surveys worth 440 million reais;
- Funding of 70 researches (R$ 65 million), selected from 529 submitted to the National Public Call for Prevention and Fight against ZIKV, a partnership between the Ministry of Health, the Ministry of Education and the Ministry of Science, Technology, Innovations and Communications;
- Support for the development of vaccines against ZIKV in Brazil, under the Oswaldo Cruz Foundation (Fiocruz), with a value of approximately 15 million reais.

THE POST-EMERGENCY MOMENT

An important front of work for the integration of surveillance and attention actions was the articulation with other developing agendas regarding congenital STORCH-Z infections. In 2017, the Interfederative Project of Rapid Response to Syphilis in care networks was developed, with the aim of reducing acquired syphilis and in pregnant women and eliminating congenital syphilis in Brazil. The project relied on resources from a parliamentary amendment, worth 200 million reais, for use by the MoH for rapid response to syphilis – Annual Budget Law (LOA) No. 13,414, published in the Federal Official Journal (DOU) of January 11, 2017. It was planned to develop actions of universal coverage and actions with 100 priority municipalities, selected from epidemiological criteria. Among the priority actions was early diagnosis and treatment, especially in pregnant women and newborns.

On **August 31, 2017**, following the request of the state of Pernambuco, the National Commission for Incorporation of Technologies in the SUS (Conitec) approved the incorporation of the drug levetiracetam for use in the control of seizures in babies with microcephaly because of ZIKV infection. This drug is considered one of the most modern for this type of treatment, already used in other countries, such as Canada and Scotland.

To continue the actions after the closure of Espin, on **December 19, 2017**, the strategy was launched to strengthen comprehensive care for children with congenital infection associated with ZIKV and STORCH, and their families. In the framework of this strategy, a series of activities was developed throughout the year 2018, which involved six prioritized states, namely: Alagoas, Bahia, Ceará, Maranhão, Rio Grande do Norte and Sergipe. The actions were organized in the following structural axes: Sexual Health and Reproductive Health; Integral Care for the Child; Integral Care for Families; and Permanent Education. This strategy also enabled the purchase of kits for early stimulation for the use of the Extended Family Health Centers (Nasf) for 4,143 municipalities, and resources to enable a complete investigation and evaluation of the development of more than 5 thousand children. These initiatives assisted states and municipalities in coping with the emergency and in organizing and preparing health services and teams.

In 2018, we sought to combine efforts and articulate the technical-political support activities of the CZS with toxoplasmosis, presenting possibilities of articulation of actions in the territories from an expanded debate with the states in training in integrated surveillance for gestational and congenital toxoplasmosis. This strategy aimed to enhance this specific agenda, but also expand the actions in the different territories, which made it possible to promote debates and proposals to the plan to reduce maternal and child mortality, which has been developed by the MoH in partnership with municipal and state managers and which has part of its actions directly related to this debate. This joint was also important so that, in 2019, toxoplasmosis was included as part of the screening collection of the National Neonatal Screening Program, the "foot test", enabling the early diagnosis of congenital toxoplasmosis.

The Zikalab Project, carried out in partnership with the Institute for Research and Support for Social Development (Ipad) and the National Council of Municipal Health Secretariats (Conasems), trained 4,192 health professionals from five FUs (Amazonas, Bahia, Maranhão, Piauí and Rio Grande do Norte) to qualify care and the organization of the care network. There was also support for the realization of the Inclusion Networks Workshops/UNICEF, held in seven UFs (Ceará, Bahia, Maranhão, Distrito Federal, Rio Grande do Norte, Alagoas and Sergipe), involving 240 professionals and families of children with CZS.

Throughout 2019, the MoH conducted joint technical visits between health surveillance and health care in the states of Pernambuco, Ceará, Bahia, Paraíba and Rio de Janeiro, whose criterion involved those with the highest number of suspected cases under investigation. We sought the strengthening of surveillance actions and the support and technical instrumentalization for the formation of state management committees for the implementation of surveillance and strategy against the actions of care of suspected children for CZS and STORCH and their families. During their visit, they were mobilized for the managers for the integration of the strategy and the strengthening of the action of the care of children with CZS and STORCH; peer-reviewed databases,

in conjunction to the SES for the final classification of the case, in particular, those in the research of children suspected of CZS; carried out the guidance and support of the management board of the State in the organization of care in the network of the children, aiming at the strengthening of the various services and points-of-care and the building of the line-of-care; and supported the coordination of intra and cross-sectoral, involving politics, health, education and social assistance. and you have been given the methodologies and tools for the diagnosis of network analysis and the recognition of the dynamics of the family.

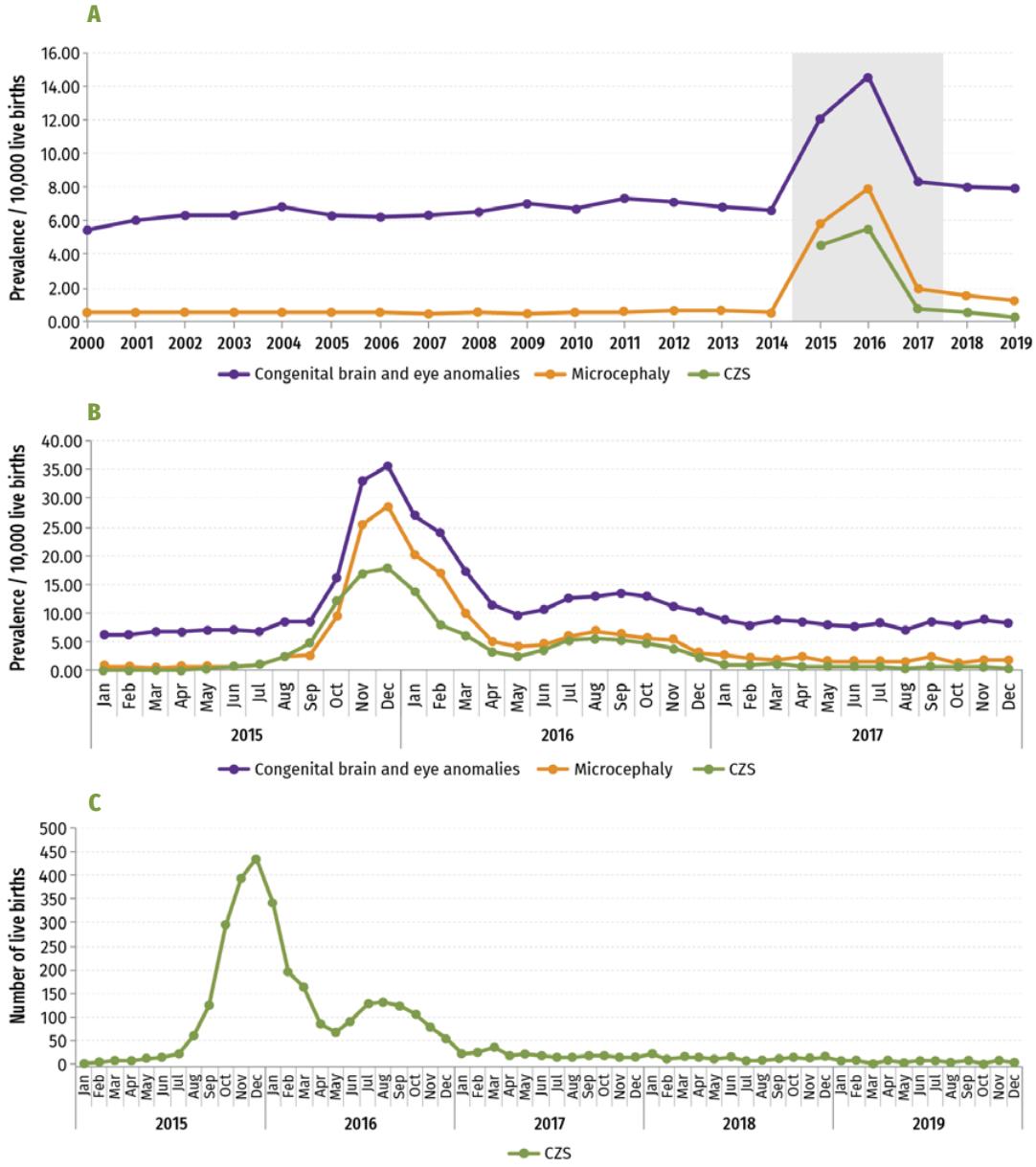
Also in 2019, the MoH promoted the formation of the Consortium of Cohorts in Zika, including 14 cohort studies in 10 units of the Federation, and counting on an investment of 18 million reais. The objective of this consortium was to promote joint data discussion and analysis of cohort studies on CZS in Brazil. Approximately 1.4 thousand children were followed, which represented about 40% of the total cases confirmed with CZS at the time. In addition, data from 2.3 thousand pregnant women were also analyzed within the framework of the consortium. This initiative enabled the analysis of the largest database related to the emergency because of CZS, since it gathered different studies that were already underway in different locations. The final studies are still being published in several journals.

EPIDEMIOLOGICAL SITUATION AND CHALLENGES FOR SURVEILLANCE

Between 2000 and 2014, the prevalence of microcephaly at birth in Brazil, based on Sinasc data, showed some stability (Graph 1A). During this period, 2,466 live births (LBs) with microcephaly were registered, with an annual average of 164 cases. In the years 2015 and 2016, the number of cases increased more than ten times compared to this average, totaling 1,758 and 2,276 LBs with microcephaly in the country, respectively. In 2015, the prevalence of microcephaly at birth was 5.83 cases per 10 thousand LBs, being even higher in 2016, with 7.96 cases per 10 thousand LBs. The increase in the prevalence of microcephaly per month of birth was observed, mainly, from October 2015 (Graph 1B). Between 2017 and 2019, the number of cases decreased again, maintaining an average of 460 cases per year, still at a higher level than in the pre-emergency period. The increase in the prevalence of live births with microcephaly in Brazil, registered in Sinasc as of 2015, was associated with ZIKV infection by different studies.[23,31]

Similar behavior was observed for the prevalence of congenital anomalies of the brain and eye (Graph 1A), possibly associated with congenital ZIKV infection. For this group of anomalies, between 2000 and 2014, there was an annual average of 1,949 records in Sinasc. In the years 2015 and 2016, the number of live births with brain and eye abnormalities increased to 3,658 (12.12 cases per 10 thousand LBs) and 4,171 (14.60 cases per 10 thousand LBs), respectively. After this period, between 2017 and 2019, the average reduced to 2,347 cases per year, but remained higher than in the pre-emergency period.

Graph 1 – Prevalence at birth of congenital anomalies of the brain and eye, microcephaly and CZS, between 2000 and 2019 (A); second month of birth in the emergency period, between 2015 and 2017 (B); and absolute number of live births with CZS*, between 2015 and 2019 (C)



Source: Sinasc, public disclosure bases. Resp-microcephaly, data updated on January 4, 2021 subject to change.

Note: CZS: Congenital Zika Syndrome. The gray area highlights the period of Emergency in Public Health of National Importance. *CZS and other infectious etiologies.

The CZS epidemic directly impacted the national registry of congenital anomalies in Sinasc, not only in the case of anomalies possibly related to the disease, but also in the increase in the registry of other anomalies.[17] Espin seems to have promoted the awareness of health professionals to

improve the registration of birth abnormalities. Despite such post-emergency improvement, several studies have reported wide spatial heterogeneity in the quality of the registration of anomalies at the national level, as well as an important under-registration of several anomalies in Sinasc.[17,32,33]

It is important to highlight that the measurements of head circumference and length at birth were not included in the DNV in the pre-emergency period. These fields were included in the form in 2016, however, they have not yet been enabled for typing in Sinasc in 2020. In addition, according to the recommendations built in conjunction with the Latin American Collaborative Study of Congenital Malformations (Eclamc), cases of severe microcephaly, that is, that head circumference less than or equal to three standard deviations below the average for age and sex, should be prioritized for registration in Sinasc.[34] This definition may explain, in part, the reduced number of records of microcephaly in Sinasc prior to spin. The adoption of more sensitive definitions during Espin led to an abrupt increase in the number of records in the system, as well as the maintenance of a higher annual average of live births with microcephaly after the closure of the emergency. In this context, the importance of updating the Sinasc to insert the head circumference and length fields at birth, in order to qualify the monitoring of live births with microcephaly in Brazil, is highlighted.

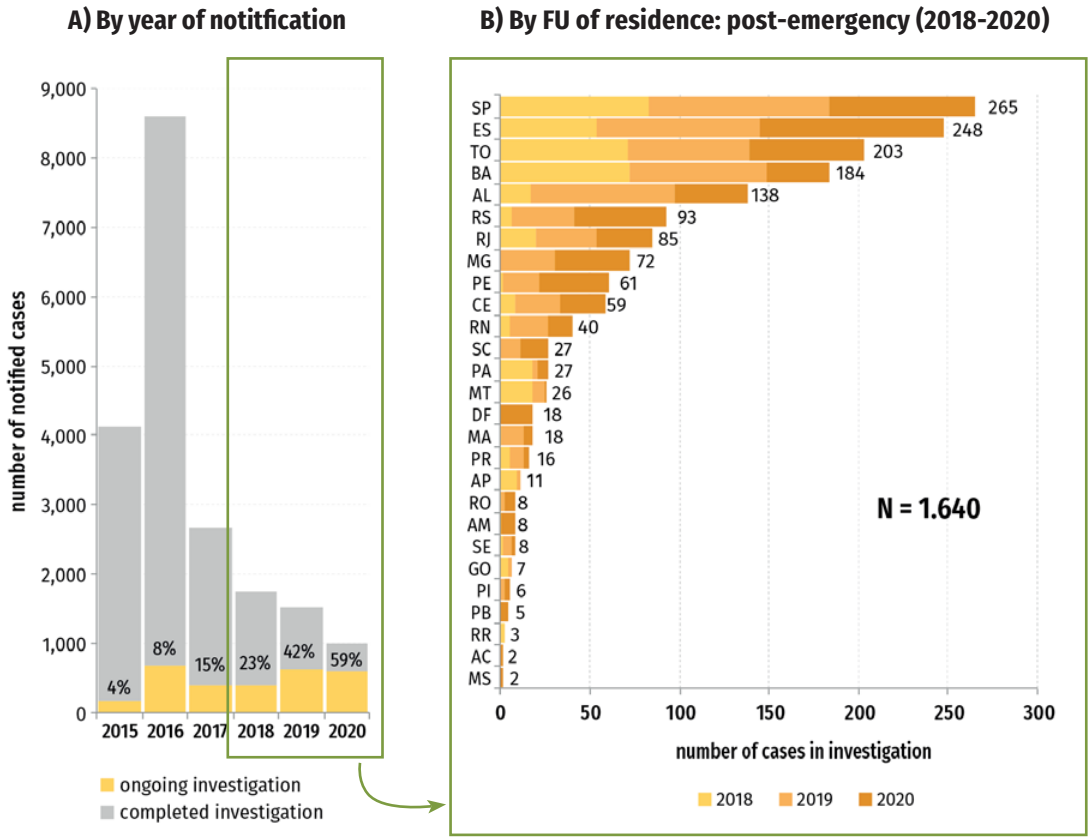
The records of live births with CZS and other infectious etiologies in Resp-microcephaly, from 2015, confirm the epidemiological scenario verified in Sinasc. Graph 1C shows the beginning of the increase in cases, especially from August 2015, characterizing an increase of three times the number of cases of the previous month (59 LBs with CZS and other infectious etiologies) and with a peak of confirmed cases in December (437 LBs with CZS and other infectious etiologies). It should be noted that, despite being made available in November 2015, the Resp-microcephaly allowed the retroactive registration of cases born from January 1, 2015. A second wave was observed in the second half of 2016, the year that presented the highest prevalence (5.51 cases per 10 thousand LBs). Between 2017 and 2019, the number of cases decreased again, however new cases of CZS continue to occur in the country.

Looking at the data shown in Graph 2A, it can be seen that an important percentage of the suspected cases registered in the Resp-microcephaly were still under investigation at the end of 2020, especially those reported in the post-emergency period. In part, this happens due to the complexity of the diagnostic process and epidemiological investigation for the classification of cases. At the end of 2020, 1,640 cases reported between 2018 and 2020 remained under investigation, representing 23% (404) of the total notifications for 2018, 42% (639) for 2019, and 59% (597) for 2020. In this period, the states that had the highest numbers of cases still under investigation, in descending order, were: São Paulo (265), Espírito Santo (248), Tocantins (203), Bahia (184) and Alagoas (138) (Graph 2B).

The high percentage of cases under investigation makes it difficult to understand the real epidemiological scenario of CZS in Brazil. A significant part of the cases of CZS remains under investigation for a long time, due to a number of reasons, such as the need to perform confirmatory tests (laboratory and imaging) and the difficulty of concluding the case by clinical-epidemiological criteria. In order to assist in this process, the integrated guidelines document recommended a second ultrasound around the 30th gestational week, in addition to the one already recommended

by the Brazilian National Health System during the first trimester to estimate gestational age. Such a recommendation had as premise allow imaging diagnosis to be performed during pregnancy, at least for the most severe cases, in which it is possible to visualize malformations such as brain calcifications and ventricular changes. The need for multidisciplinary work is also highlighted, considering that the surveillance process of the CZS encompasses different knowledge and practices.

Graph 2 – Distribution of cases under investigation for Congenital Zika Syndrome and other infectious etiologies by year of notification (A) and by FU of residence of the post-emergency period (B). Brazil, 2015-2020



Source: Resp-Microcephaly. Data updated as of January 4, 2021, subject to change.

In addition, it is common to have a loss of follow-up by the surveillance team, especially when the child is not being followed by the public health network or when they participate in some research project. For this reason, the integrated guidelines document included the possibility of classifying the case as inconclusive, so that the health authorities could close the case due to loss of follow-up or refusal by the family. However, it should be emphasized that the research process must go simultaneously with the assistance to the child and his family, starting timely early stimulation and offering the necessary services.

From the face of Espin, it was identified the need to integrate the available information on congenital anomalies in different information systems of the MoH. Each system has its own specific case definitions and work processes, which sometimes makes it difficult to jointly analyze the data. For example, there is a need to revise the recommendations for coding deaths from CZS in the Mortality Information System (MIS). WHO has already made available an updated version of ICD-10, which includes code P35.4 for congenital ZIKV disease. The inclusion of this specific code in the SIM, as well as standardization of the coding of these deaths, is essential for the correct capture of deaths associated with CZS and to qualify mortality statistics for this cause in the country.

It is also important to consider that the Sinasc captures the cases of congenital anomalies identified at birth, while the SIM records the anomalies that contributed to death. Resp-microcephaly is currently the only tool that captures congenital anomalies diagnosed after birth and before death, although limited to CZS and other infectious etiologies. However, it is important to consider that the Resp-microcephaly is an electronic form, with limited resources and that lacks more robust functionalities inherent to health information systems. Thus, it is understood that, in addition to strengthening existing systems, it is essential to develop a robust information system that allows the registration of congenital anomalies diagnosed throughout life, interoperable with other systems.

FINAL CONSIDERATIONS

After more than five years of Espin due to the increase in the occurrence of children born with microcephaly in Brazil, there are still questions to be answered and the need for monitoring is constant. The researches that are still in progress seek to answer these questions and help in the characterization of this new syndrome, in the identification of its epidemiology, as well as in the improvement and elaboration of new health policies. It is important to emphasize that children with CZS continue to be born in Brazil and, despite the quantity being much lower than in the period of Espin, the health system cannot fail to carry out adequate epidemiological investigation and referral to health services in a timely manner.[35]

Over these years, the actions and recommendations have been constantly modified to suit the new evidence. The very late notification of children was later recommended when it was realized that some signs and symptoms were not easily identified or developed soon after birth. Therefore, all health professionals and services needed to be more attentive to the suspicion of a possible diagnosis. This process potentiated the integration of attention and surveillance actions, since care professionals were sensitized and had their role as a sharp investigator and allowed the teams to integrate so that epidemiological investigation and clinical diagnosis could be carried out simultaneously. This integrated process was not routine in most services and taught SUS a lot, expanding the capacity to respond to an emergency of this magnitude.

States and municipalities were key factors in the emergency response. The articulation of the three spheres of Health System Management enabled the development of different work fronts, including health surveillance, health care, teaching and research. In addition, other actions, in an intersectoral way, were developed and mobilized society as a whole, involving many and different actors in the Brazilian response to this public health emergency, the first Espin declared by the federal government. The maintenance of intersectoral public policies to guarantee social rights of children and their families is also a challenge and still today makes up the agenda of social protection policies.

As part of the organization of the health system and policies, a great challenge that this emergency brought to the SUS was the organization of sexual health and reproductive health actions for women and men in all life cycles, seeking to qualify the prevention of new cases of transmission of ZIKV and STORCH, its consequences and related diseases. Thus, the expansion of the agenda regarding surveillance and attention to congenital anomalies could be potentiated by seeking to qualify the processes of reproductive planning, prenatal and puerperium.

In this perspective, it is important to strengthen the articulation and integration between surveillance and primary care, as well as the articulation of the care network as a whole. The aim is to expand access to complete diagnosis, treatment and rehabilitation of children with CZS and other congenital anomalies, ensuring access and articulation of the care network for the integrality of care. Similarly, investments are important for regional health systems to enable actions and health services to follow the growth and development of these children. This is a great challenge, because in general, children born with some anomaly require care, from corrective interventions to rehabilitation, and often require access to more complex services for long periods.

From the beginning of the emergency, it was noticed that the microcephaly notification data in Sinasc were not representative. In the post-emergency period, it became clear the need to keep active surveillance of new cases of CZS that continue to emerge in the country[35] in addition to the urgency of implementing a national program for the surveillance of congenital anomalies. This agenda has been built seeking articulation with the set of policies and protocols in force that have convergence with this proposal of congenital anomalies surveillance. In addition, it seeks to strengthen the registration of anomalies in Sinasc, which is prominent in an international context as one of the largest information systems on live births in the world. The integration of information systems and records of events in health, within the MoH, can enrich the information available at birth and, in light of the concept of triple surveillance of congenital anomalies, contribute to the monitoring of risk or causal factors and outcomes, such as hospitalizations or even cases of death.

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12

FROM THE PUBLIC HEALTH EMERGENCY OF MICROCEPHALY TO THE SURVEILLANCE OF CONGENITAL ANOMALIES: THE PERNAMBUCO EXPERIENCE

SUMMARY

OBJECTIVE

To describe the strategy of Pernambuco in the public health emergency related to microcephaly and characterize the implementation of surveillance of other congenital anomalies of infectious etiology.

METHODS

This is an experience report built from the review of available official documents on the Public Health Emergency of National Importance by changing the pattern of occurrence of microcephaly in Brazil, focusing on the experience of the state of Pernambuco and reports of local managers.

RESULTS

In October 2015, the state of Pernambuco was the first place to identify the change in the pattern of occurrence of births of children with microcephaly. In Pernambuco, the abrupt increase in births with this condition occurred simultaneously with the Zika virus epidemic. The unusual situation and the risk of national and international dissemination led to the outbreak of the Public Health Emergency of National and International Importance. The arena that involved the political decisions for the construction of a response to this emergency permeated by the composition of diverse actors and institutions. The responses of surveillance and health care in the emergency situation of microcephaly differed in intensity and time due to the structural nature required for each area.

CONCLUSION

The surveillance of congenital Zika syndrome and other infectious etiologies is changing the paradigm and requires broad discussion and understanding of this integrated approach process.

KEYWORDS

Microcephaly. Public health. Health assessment. Emergency situation.

INTRODUCTION

The spread of infectious diseases is a long-standing public health problem. With the advent of globalization, this phenomenon intensified the ability to penetrate world borders due to the large number of travel and international trade in goods. As a result, health surveillance has gained a crucial character in the monitoring of emergencies related to national and international public health.[1,2]

Brazil, since 2006, has been adapting to cope with these emergencies. The Unified Health System (SUS) implemented technical instances of readiness and response to these events, such as the Strategic Health Surveillance Information Centers (Cievs), the national force of the Unified Health System (FN-SUS), the Network of Border Laboratories and the Interministerial Executive Group of Emergency in Public Health of National and International Importance.[1,3,4]

Cievs is part of the Global Outbreak Alert and Response Network (Goarn) and is included in the national health surveillance guidelines.[5] Its main tasks are detection, truthfulness assessment, monitoring and sharing of updated epidemiological information to identify early risks and emergencies in public health, as well as coordinated response.[6]

In Pernambuco, the State Health Department (SES) began the implementation of Cievs-PE in 2007 and, in 2009, formalized the structure of the service. Its work involves the monitoring of diseases of immediate compulsory notification, coping with public health emergencies and risk assessment in mass events. The state Cievs acted on events such as the influenza pandemic (2009); the occurrence of Klebsiella pneumoniae, producer of carbapenemase (2010); the floods of the Southern Forest (2010 and 2011); the measles outbreaks (2010 and 2014); the mass events such as Confederations Cup (2013), World Cup (2014), Carnival (2012-2019); and the preparation for the face of the Ebola virus (2015). With the advent of the increase in the occurrence of microcephaly, it was up to the Cievs of Pernambuco to evaluate the event and trigger the response process to the Public Health Emergency (ESP) triggered internationally.[6]

Brazil contributed 89.8% of confirmed cases of microcephaly associated with the Zika virus in the world, until January 2017. Pernambuco presented, between the epidemiological weeks 45/2015 and 52/2016, a prevalence of microcephaly of 23.9 per 10 thousand live births (LBs), higher than the other federated units (UFs) of the country that were affected by the epidemic in the same period.[7]

In order to contribute to the strengthening of the Unified Health System (SUS), and considering that Pernambuco was the initial point of ESP and led the construction of Public Strategies to deal with this situation, this report of experience aims to describe the performance of the health system in the state of Pernambuco during ESP related to microcephaly, and characterize the implementation of surveillance of other congenital anomalies of infectious etiology.

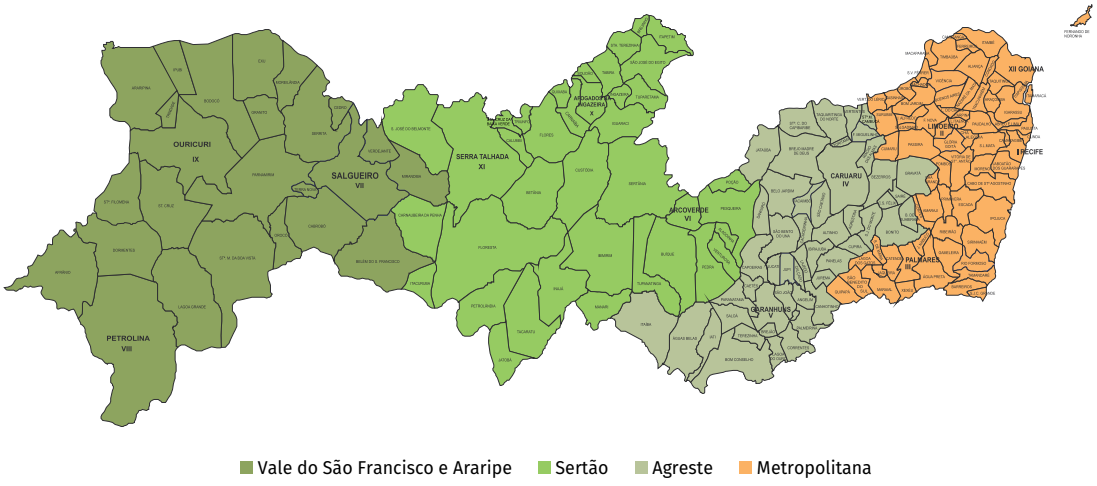
METHODS

This is an Experience Report built from the review of official documents available on the Public Health Emergency of National Importance (Espin, in Portuguese) by changing the pattern of occurrence of microcephaly in Brazil, focusing on the experience of the state of Pernambuco. In addition, the experiences of the managers of the State Health Department of Pernambuco, authors of this chapter, who acted during the emergency response were reported.

Pernambuco is a Brazilian federated unit, located in the Northeast region, bordering the states of Paraíba, Ceará, Piauí, Bahia and Alagoas and, to the East, the Atlantic Ocean. It has a territorial extension of 98,146.315 km^2, divided into 184 municipalities and the State District of Fernando de Noronha. It is the seventh most populous state in the country, with an estimated 9,345,173 inhabitants, for the year of 2015, being about 80.0% urban residents.[8,9]

The state of Pernambuco has a wide care network, with 57 hospitals, located in four macro-regions, most of them in the capital, Recife, as well as decentralized surveillance services in 12 regional management (Figure 1) and the Center for Strategic Health Surveillance Information (Cievs-PE) installed at the central level of the state and in the capital. The 2,100 primary care teams are managed by the Municipal Health Secretariats (SMS).[8]

Figure 1 – Macroregions (Macro) and Regional Health Management (Geres) of Pernambuco



Source: SES/PE[25].

This article was organized into six sections: 1) the Zika virus; 2) detection of microcephaly; 3) Pernambuco's response to the microcephaly event; 4) emergency management; 5) actions taken in the state in relation to health surveillance; and 6) surveillance of other congenital anomalies of infectious etiology.

RESULTS AND DISCUSSION

The Zika virus

In 2015, the Zika virus was first identified in Brazil by researchers from Universidade Federal da Bahia (UFBA). The circulation of the Zika virus in Pernambuco was confirmed in July 2015 in the samples of four patients living in the municipalities of Jaboatão dos Guararapes, Recife and Olinda, who presented the first symptoms in March 2015.[10]

In July 2015, the State Health Department of Pernambuco (SES-PE) published a technical note guiding the surveillance and health care services for the local circulation of the Zika virus.[10] As a new disease in the national territory, the actions focused on the implementation of surveillance of the Zika virus, the detection of the occurrence of acute cases, the characterization of the epidemiological profile of laboratory-confirmed cases and the monitoring of the occurrence of atypical manifestations.

At that time, the challenges arising from the circulation of the Zika virus were not yet fully clarified. However, some situations were already configured, such as the overlap of cases of Zika virus with the epidemic of dengue and chikungunya,[11] the insufficient availability of laboratory diagnosis, the increased occurrence of cases of neurological diseases, which subsequently showed a relationship with the Zika virus,[12] and the increase in births of children with microcephaly, which, unusually, showed a spatial and temporal association with the occurrence of the Zika virus in Pernambuco.[13]

Detection of microcephaly

On October 22, 2015, the State Health Department of Pernambuco was informed by the Maternal-Child Network about the increase in births of newborns with microcephaly. Promptly, the rumor was investigated by Cievs, which found the registration of 29 cases in the Live Birth Information System (Sinasc), occurred between August and October of the said year. The verification in the Sinasc records characterized a change in the pattern of occurrence of these congenital changes, with an increase in the number of cases compared to the months from January to September of the previous years, being, respectively: 5 cases (2011), 9 (2012), 10 (2013), 12 (2014) e 20 (2015).[14] From that moment, the largest response operationalization to an ESP experienced in Pernambuco began.

The communication of the event to the Ministry of Health occurred within 24 hours from the observation of a potential Emergency in Public Health of National Importance (Espin). The previous establishment of communication flow of the CIEVSP with the Ministry of Health enabled agility in the investigation of the event by the National Authority.

With the expansion of the investigation of the event to the other federated units of the country, more cases began to be detected, especially in the Northeast Region. On November 11, 2015, the Brazilian government declared an Emergency in Public Health of National Importance and, on the 28th of the same month, confirmed the relationship between the Zika virus and the

microcephaly epidemic.[6] The state of Pernambuco decreed Public Health Emergency of State importance on November 29, 2015;[15] while the World Health Organization (WHO) declared the Public Health Emergency of International Importance (Espii) on February 1, 2016.[16] These normative acts formalized a period of 10 months of Espii and 20 months of Espin confrontation.[17]

As a documentary landmark, SES-PE issued, on October 27, 2015, the Technical Note Sevs/DGCDA No 43, which addressed the possible change in the pattern of occurrence of microcephaly (congenital anomaly) in live births in the state of Pernambuco. At the time, immediate notification of suspected cases was established through Cievsp, the sector responsible for monitoring the event at the state level.

The historical series of notifications for congenital Zika syndrome (CZS) of residents in Pernambuco, between the epidemiological week (SE) 30/2015 and 53/2020, presents a total of 2,931 reported cases (Table 1).[18] It is observed that 76.3% (2,236) of the reported cases and 90.4% (425) of confirmed cases occurred in 2015 and 2016.

Table 1 – Number and percentage of cases of congenital Zika syndrome, according to final classification and year of notification, Pernambuco, SE 30/2015 to SE 53/2020[18]

	YEAR OF NOTIFICATION											
	2015		2016		2017		2018		2019		2020	
CLASSIFICATION	N	%	N	%	N	%	N	%	N	%	N	%
Confirmed	266	23.1	159	14.6	20	10.4	18	9.3	7	3.7	0	-
Discarded	835	72.7	869	79.9	151	78.2	149	76.8	137	72.5	80	67.3
Inconclusive	48	4.2	59	5.5	22	11.4	27	13.9	25	13.2	6	5.0
Under Investigation	0	-	0	-	0	-	0	-	20	10.6	33	27.7
Total	**1149**	**100**	**1087**	**100**	**193**	**100**	**194**	**100**	**189**	**100**	**119**	**100**

Source: Resp/SES-PE.

It is important to highlight the high number of children with confirmed diagnosis of CZS, with 23.1% in 2015 and 14.6% in 2016. Similar frequency was described in a study that analyzed the notifications made in the country between the years 2015 and 2016, which pointed to a confirmation rate for CZS of 24.4% and 16.5% in Brazil, in the respective period.[16]

The reduction in the notification and confirmation of post-epidemic cases was in line with studies conducted in Brazil and Southeast Asia, with the highest number of notifications in the epidemic period, with subsequent reduction and stabilization.[16] This trend has also been observed in the Zika virus fever epidemic in Southeast Asia.[19]

Table 2 shows the characterization of cases of CZS according to the type of notification, gender and WHO standardized definition (microcephaly and severe microcephaly) corresponding to the period of 2015 and 2016. The prevalence of the type of notification "newborn with microcephaly (≤ 28 days)" was observed in 2015 and 2016, respectively, 1,145/99.7% and 1,003/92.3%. Regarding sex, it was observed that the female sex is the most affected (2015: 718/62.5%; and 2016: 664/61.1%), in a sex ratio of 1.7 girls to 1.0 boys, in 2015 and 2016.

In order to characterize the cases of CZS according to the WHO standard definition, the present analysis used the number (N) of records corresponding to children classified with microcephaly and severe microcephaly, excluding those who did not meet the case definition established in the guidelines for epidemiological surveillance of Congenital Zika Syndrome in the state of Pernambuco and those who were not informed. Thus, in 2015, 208 (18.1%) cases of microcephaly were identified and 224 (19.5%) with severe microcephaly. In 2016, there was an increase in the percentage of records as microcephaly, with 396 cases (36.4%), and 197 (18.1%) were classified as severe microcephaly (Table 2).

Table 2 – Number and percentage of cases of Congenital Zika Syndrome, according to notification type, sex and characterization of microcephaly, Pernambuco, 2015-2016

VARIABLES	2015		2016	
	N	%	N	%
Type of notification	**1,149**		**1,087**	
Newborn with microcephaly (<=28 days)	1,145	99.7	1,003	92.3
Child with microcephaly and/or CNS disorders (>28 days)	1	0,1	39	3,6
Stillbirth with microcephaly and/or changes in CNS	3	0,3	45	4,1
Sex				
Female	718	62.5	664	61.1
Male	430	37.4	401	36.9
Not informed	1	0.1	22	2.0
Characterization of the presence of microcephaly				
Severe microcephaly	224	19.5	197	18.1
Microcephaly	208	18.1	396	36.4
Does not meet the definitions	705	61.4	400	36.8
Ignored	12	1.0	94	8.6

Source: Resp/SES-PE.

The number of notifications and confirmed cases in the state made Pernambuco occupy a prominent place in the epidemic and post-epidemic scenario, being of fundamental importance the action of the public authorities to cope with it.

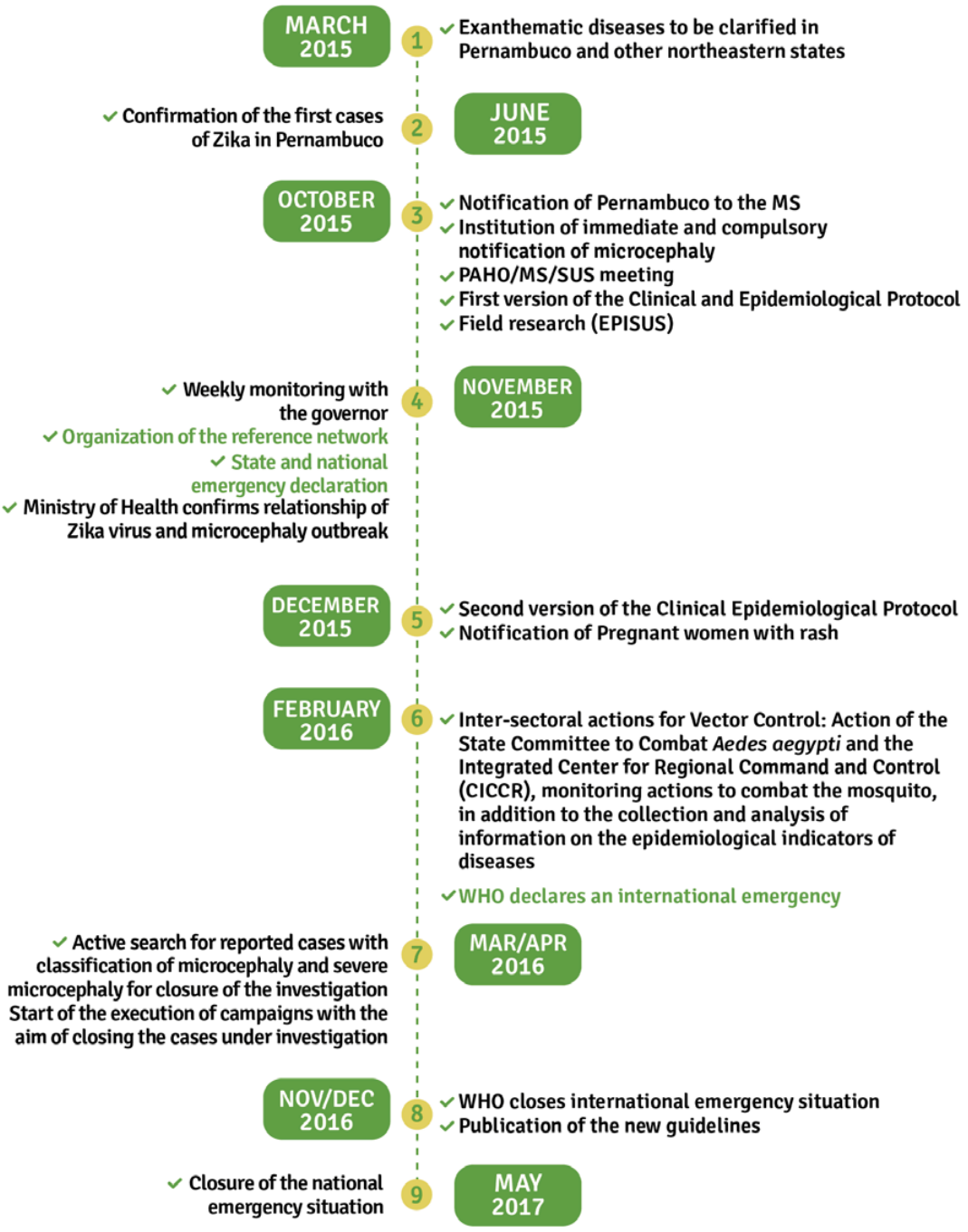
Pernambuco's response to the microcephaly event

Also in 2015, investigations were started to better understand the etiology of microcephaly cases and, in a short time, its association with maternal infection by the Zika virus was verified.[6,20,21] From this fact, intersectoral work was established for the development of several prevention and care actions, as well as research and education. Figure 2 presents the timeline of facts of the microcephaly public health emergency.

With the active search for data and as the investigation evolved, it soon became clear that microcephaly was only an initial feature that aroused the attention of health professionals. Promptly, a set of signs and symptoms, which included microcephaly, was detected in newborns whose mothers presented exanthematic picture compatible with Zika virus infection. This set of signs and symptoms came to be called congenital Zika syndrome.

To describe the response to microcephaly in Pernambuco, it is necessary to highlight three pillars: management, surveillance and health care.

Figure 2 – Microcephaly public health emergency timeline



Source: authors.

EMERGENCY MANAGEMENT

The arena that involves political decisions for the construction of a response to a problem of this nature permeates through the composition of diverse actors and institutions. Recognition of the relevance of the problem occurs in processes whose scenarios are characterized by conflicts of interest of groups, doubts and uncertainties.[22]

The response counted on different professionals and institutions involved in the management of the event. At the governmental level, the state sphere had the partnership of the Ministry of Health, the Pan-American Health Organization (PAHO) and municipal representatives. In addition to these, technical groups and specialists in health and other extra-health began to integrate the event management group as representatives of universities, research institutions, Social Security and assistance, the Department of Education, the Army, the Civil House, among others. Despite not having a seat at the decision-making table, the media and social mobilization were active influencers in the decisions adopted.

In this process, the institution of the Public Health Emergency Operations Committee (Coes), consisting of a team of multiple institutions and professions, was highlighted, which strengthened the capacity to respond to the public health emergency by aggregating the experience, technical knowledge and scientific support of researchers.[23] With the institution of the Coes, administrative and normative acts had speed and guidelines for surveillance and health care actions emerged, as well as strategies for dialogue with society through the management of risk communication.

Communication with society and health professionals was another aspect that required a lot of commitment from the SES-PE. The local and international press and the management of rumors demanded the constant production of information and technical professionals and experts who represented and were available to clarify the questions posed. Other actions are highlighted, such as the realization of training provided to the local press; the definition of spaces (physical and virtual) and means communication and dissemination of information (official of extraofficial); and the establishment of the flow of communication with the media.

The insertion of scientific research was a necessity noted at the beginning of the epidemic. The hypothesis of association of congenital anomalies with the Zika virus was not a process described in the scientific literature. To confirm or refute this hypothesis, investments were directed to the development of clinical and epidemiological research. However, issues related to the research were not limited to its development, so it became necessary to manage institutions and researchers who requested, in dimensions never experienced by local management, data and access to patients. It was then adopted to add to the management group researchers who contributed to the establishment of criteria for the release of local consent to research.

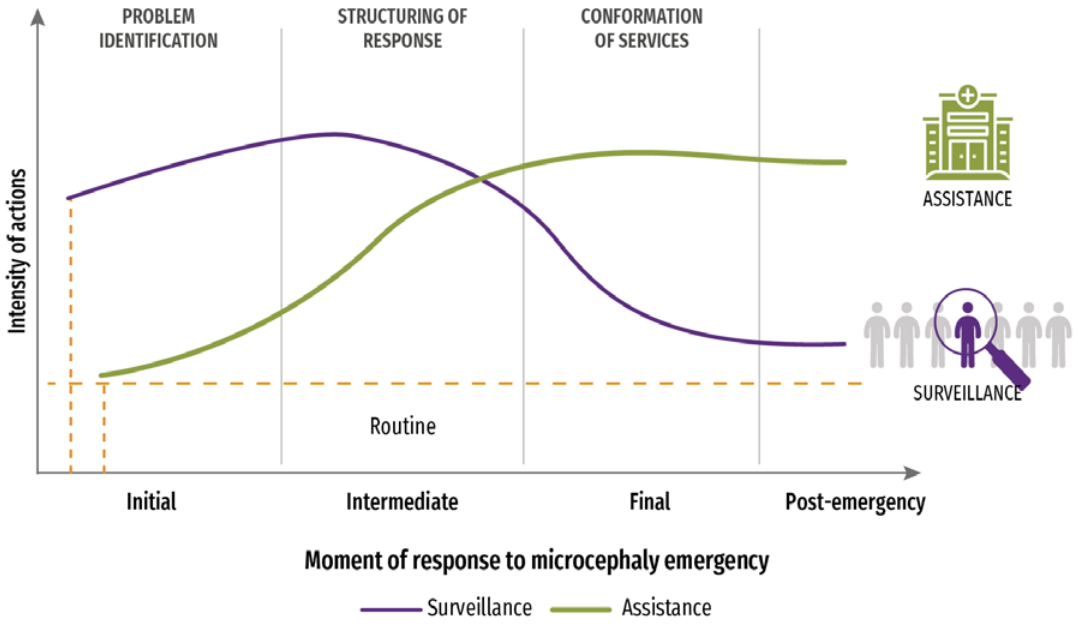
Another important milestone was the creation of the Support Center for Families of Children with Microcephaly (NAFCM), implemented in May 2016. The NAFCM was conceived with the aim of decentralizing the management of microcephaly to the 12 Regional Health managements (Geres) of Pernambuco, with the scope of coordinating, monitoring and supporting regionalized actions

of active search, diagnosis, rehabilitation and follow-up of children notified with the CZS and assisting their families. With the perspective of transversality of care, the nucleus works in an intersectoral way, articulating actions with education for the inclusion of children in the school network and with social assistance, in order to minimize situations of vulnerability.

SURVEILLANCE AND HEALTH CARE ACTIONS

For the description of the actions of surveillance and health care, we opted for the graphic construction of a timeline of the organization of the response of the sectors. The intensity and speed of implementation of the actions occurred in a distinct way until the real need of the target audience and the structuring of the work of these sectors were formed (Figure 3).

Figure 3 – Illustrative representation of the evolution of the response to the public health emergency of microcephaly. Pernambuco, October 2015 to July 2017[24]



Source: Adapted from Aguiar *et al.* (2020)[25].

At the beginning of the ESP, the decision arena directed most of the propositions for the rapid response of surveillance, in order to ensure the detection of cases to measure and characterize the event in the clinical-epidemiological aspects and to allow the feeding of local, national and international governmental bodies with timely information. Health care actions focused on supporting surveillance actions. At this time, the efforts were centralized in the reference services in the capital, with expansion of care and diagnosis beyond the routine.

In the intermediate phase (Figure 3), the decision of the monitoring was to be directed to the suitability of the worker process (detection, reporting, investigation, and management of pregnant women with rash and suspected cases of microcephaly, intrauterine and postnatal), and the design of the services, disease surveillance, hiring, and training of human resources, surveillance, laboratory (stream, sampling and preparation for analysis), and the Verification of Death (research etiological of stillbirths), as well as the support of the municipalities are at risk for the arboviruses.

The care solutions, in the intermediate phase, were directed to the decentralization of care in the four macro-regions of the state, with an expansion from 2 to 32 care units for children with microcephaly, in the period from 2015 to 2017.[11] The actions related to newborns with microcephaly were directed to the hospital (Anamnesis, physical and imaging examination, ophthalmological evaluation), out hospital (specialized evaluation, echocardiogram, otoacoustic emission, among others) and diagnostic care for pregnant women with rash, with the support of the municipalities. In addition, campaigns were performed for care in regions with specialized care gaps or in those with accumulation of notifications without diagnostic definition.

In the third stage (Figure 3), the deliberations were structural in nature for the services, given the rise of complex and higher cost activities. The decisions were aimed at consolidating the assistance services in the macro-regions and strengthening the coordination, monitoring of the care line and structuring the network for the post-emergency period. The assistance focused on the formation of the clinical care network, diagnosis, rehabilitation and regulation of specialized procedures. In surveillance, the priority was the speed of laboratory diagnosis, the closure of cases with delayed investigation, the establishment of a technical area of surveillance of Congenital Zika Syndrome and the monitoring panel of arboviruses and CZS.

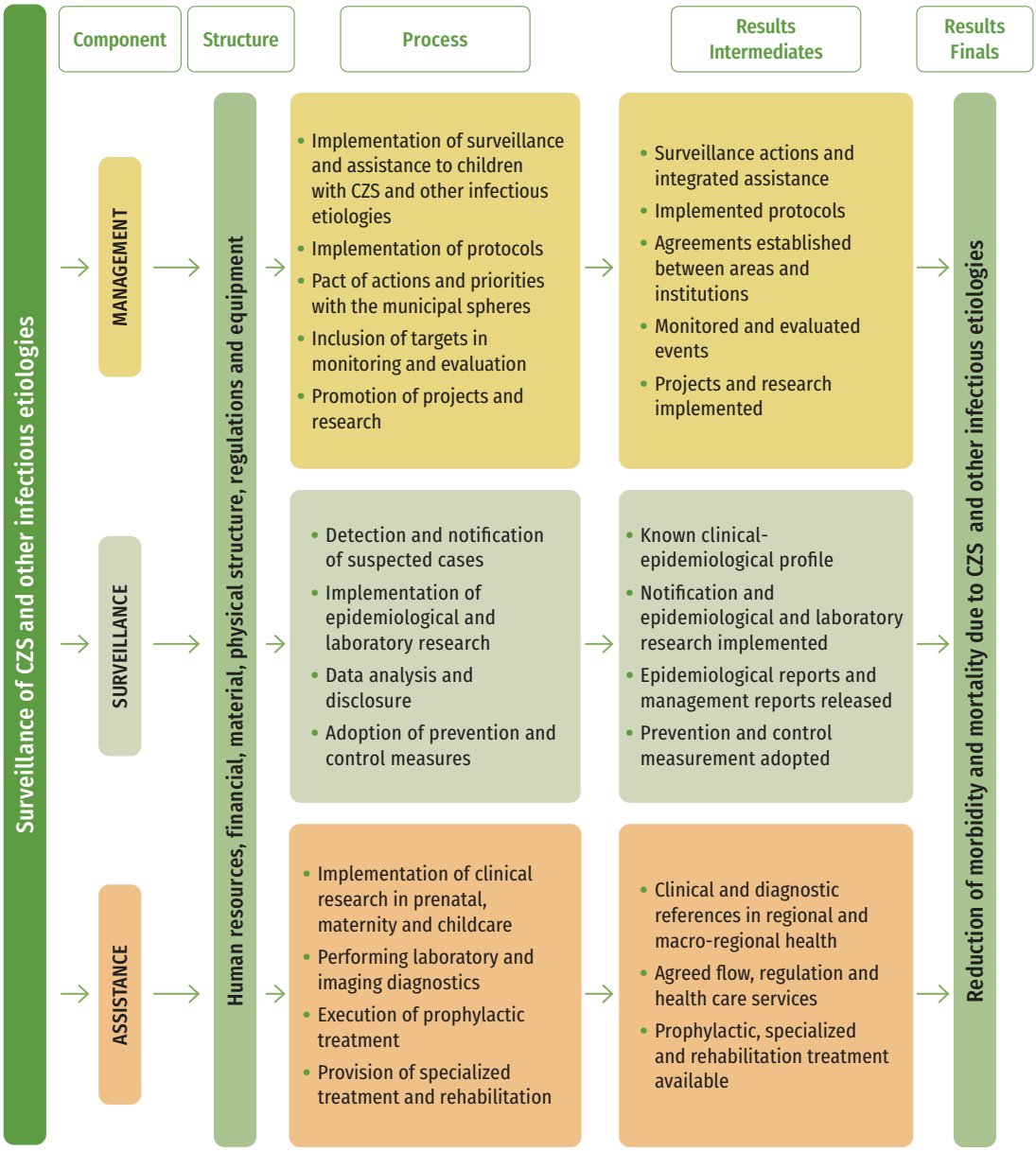
SURVEILLANCE OF OTHER CONGENITAL ANOMALIES OF INFECTIOUS ETIOLOGY

Five years after the onset of PEs of microcephaly, the actions triggered were configured and, in 2017, began the structuring of surveillance of CZS and other infectious etiologies, such as those caused by syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex, whose initials form the STORCH acronym.

Surveillance of CZS and other infectious etiologies (STORCH) is changing the paradigm for an integrated approach, since it performs many functions using similar structures and work processes. Currently, this surveillance is based on indicators, which consists in the collection, analysis and interpretation of structured data, for the purpose of risk assessment for Public Health and dissemination of control and prevention measures. However, special efforts are needed to design quality indicators for integrated surveillance of CZS and other etiologies, considering the development of universal and specific indicators for each disease, since they require different surveillance data.

The construction of this structure and the working processes of surveillance is essential for the control of congenital transmission of the Zika virus and the reduction of its damage in newborns. In this sense, a logical model was developed as a systematized evaluation tool that can generate important contributions to the integrated surveillance of CZS and other infectious etiologies (Figure 4).

Figure 4 – Logical model of surveillance of CZS and other infectious etiologies in a state instance



Source: adapted from Aguiar *et al.* (2021).[27]

Note: CZS – Congenital Zika Syndrome associated with the Zika virus infection.

FINAL CONSIDERATIONS

The ability of the Zika virus to cause congenital malformations was unknown until the occurrence of the epidemic in Brazil. Its complications are characterized as an important public health problem, with social and economic impact related to the health care of affected children and their families.

The integral and continuous monitoring of the CZS profile is essential for the characterization of the event. Integrating CZS surveillance with established ones (congenital rubella syndrome and syphilis) and some in implantation (toxoplasmosis, cytomegalovirus, herpes simplex) will require political commitment, adequate financial support, as well as broad discussion and understanding of this integrated approach process. However, the effort should focus on the availability of information for action, and this will require similar core activities (case detection, notification, epidemiological investigation, confirmation, analysis, interpretation and action) and support functions (epidemiological standardization, training, laboratory support, provision of specific treatments, supervision and financial support).

There is no doubt that many lessons have been learned from the response to the emergence of microcephaly. This report of experience highlights the journey of a new surveillance that was born from the detection of an unusual event in Pernambuco and that needs to ensure its space in the public health agenda. Therefore, the mission of the three spheres of government (federal, state and municipal) that make up the Unified Health System is to ensure public policies that allow the population to have universal, integral and equitable access to health.

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13

CONGENITAL ANOMALIES IN THE LIVE BIRTH INFORMATION SYSTEM, 2001-2020: REPORT OF EXPERIENCE OF THE MANAGEMENT OF THE SYSTEM IN THE CITY OF SÃO PAULO

SUMMARY

OBJECTIVE

To report on the actions developed by the managers of the Live Birth Information System (Sinasc, in Portuguese) of the Municipal Health Department of São Paulo (SMS-SP), in the period from 2001 to 2020, to increase the notification of congenital anomalies (CAs) and improve the completion of the fields of the Live Birth Declaration (DNV, in Portuguese) in the municipality.

METHODS

A documentary analysis of the records of actions carried out by the management of Sinasc in the city of São Paulo, from 2001 to 2020, aimed at promoting the registration of CA and improving the quality of filling in the DNV was carried out. This report is also based on the experience of the Sinasc managers in the municipality, authors of this chapter. To demonstrate the evolution of reporting and data quality, the Sinasc historical series from 2001 to 2020 was analyzed.

RESULTS

Between 2001 and 2020, several actions were carried out: visits to public and private hospitals and maternity hospitals in the municipality, which, over the period, reduced 120 to 84 establishments; training courses in the diagnosis and registration of Chas, production of didactic and informative material; continued care and close contact with maternity teams; and institution of the Sinasc Seal to reward work excellence. The main result of these actions is shown in this chapter: the decrease in the absence of filling in field 6 of the DNV, with rates around 25% at the beginning of the historical series that reached practically 0%, and the notification from 0.4% to 2% of CA.

CONCLUSION

The adoption of continuous practices and actions of the municipal management of Sinasc with maternity hospitals promotes adequate notification of Chas, essential to implement monitoring and surveillance systems.

KEYWORDS

Congenital anomalies. Born alive. Information system. Vital statistics.

INTRODUCTION

Congenital anomalies (CAs) are changes in embryofetal development, morphological and/or functional present since prenatal life and identified at this stage, at birth and until later, in adulthood.[1] They constitute a major public health problem in a number of respects: a) it is estimated that about 300 thousand newborn babies die before the 28th day of life, all around the world every year, due to CAs; b) they, in general, can contribute to different kinds of disabilities or impairments in the course of a lifetime, with significant consequences for affected individuals, their families, and health care systems, and society; c) in the majority of cases, the cause is not identified, and on the other, genetic factors, infectious agents, or dietary exposure to teratogenics to environmental are cause factors; d) some of the CAs can be prevented by using a variety of approaches, such as vaccination; supplementation or fortification of food and prenatal care, proper identification of risk factors.[1]

Since 2010, the World Health Organization (WHO) has developed several recommendations for CA surveillance. In the document of the 63rd World Health Assembly in 2010,[2] among the various actions for a national program for the prevention and care of CAs, WHO includes the establishment of appropriate surveillance systems for these conditions. To do so, which, in the implementation of these systems, you can obtain support through the collaboration with the monitoring systems, such as the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), the Study is a Collaborative Perception of Congenital Malformations (Eclamc), an International Database of Craniofacial Anomalies (IDCFA) of the WHO, and the European Registration of Congenital Anomalies (EUROCAT).

The Live Birth Information System (Sinasc) was implemented in Brazil by the Ministry of Health (MS) in 1990, with the aim of recording information regarding all live births in the national territory, allowing the construction of indicators on prenatal care, childbirth and epidemiological profile of live births and mothers.[3]

Since the 2000s, several studies have been published on the prevalence and Risk Factors of CAs in Brazil. Although there are descriptions in several units of the Federation (UFs), most of them are based on small observational, hospital-based and retrospective samples.[4-7] Works with more representative samples, involving more than 30 thousand births, were also published.[8-10] Based on data contained in the Live Birth Declaration (DNV, in Portuguese), an analyzed sample of 41,838 newborns from the Vale do Paraíba Paulista revealed that in 1.5% there was no filling in the field corresponding to the congenital anomaly, and 0.76% of the records had at least one CA.[8] The situation of high number of DNV without filling in field 6 or with low registration of them (prevalence less than 1%) has also been observed in other studies.[9,10]

At least a dozen articles report the prevalence of CA, based on Sinasc records, with large samples. One of them analyzes the births that occurred in Rio Grande do Sul,[11] in the period from 2005 to 2014. There were 1,386,803 live births (LBs), and the overall mean prevalence of cases diagnosed with CA was less than 1% (0.92%). The article “Qualidade da notificação de anomalias congênitas pelo Sistema de Informações sobre Nascidos Vivos (Sinasc): estudo comparativo nos anos 2004 e 2007” goes beyond the simple observation of the prevalence at birth of CAs.[12]

The authors compared the registration of cases of LBs with CA in seven maternity hospitals in several Brazilian cities in two years: 2004 and 2007, with expressive samples of 27,945 and 25,907, respectively. These records were compared, in the same maternity hospitals, to the hospital-based record of Eclamc, considered gold-standard. The results indicated that, in 2004, at least 40% of CAs were not registered and that this situation remained in 2007. They conclude by noting the need for investments to improve the quality of the notification of CAs in Sinasc.

The objective of this work is to report the actions developed by the management of Sinasc of the Municipal Health Department of São Paulo (SMS-SP), in the period from 2001 to 2020, to increase the notification of CA and improve the completion of the DNV fields in the municipality.

METHODS

A documentary analysis of the records of actions carried out by Sinasc managers in the city of São Paulo (MSP), from 2001 to 2020, aimed at promoting the registration of CA in Sinasc and improving the quality of filling in the DNV was carried out. This report is also based on the experience of the Sinasc managers in the municipality, authors of this chapter.

Since the implementation of Sinasc in MSP, in 2000, the establishments that perform births fill in and enter the DNV directly in the computerized application, which facilitates data collection, minimizes underreporting and, especially, the time lag of the registry. The information for completing the DNV is collected by nursing and/or administrative professionals, by consulting the medical records and interviews with mothers.

To demonstrate the evolution of notification and data quality in field 6 of the DNV, the proportions of registration (presence of CA) and absence of information (ignored and unfilled) in the Sinasc historical series from 2001 to 2020 were analyzed.

RESULTS

Sinasc SMS-SP, since its implementation, has established channels of permanent communication with hospitals/maternity hospitals for guidance and clarification of doubts, both in person and at a distance (telephone, e-mail, others).

As of 2005, the Coordination of Research and Information (CEInfo)/Management from the Sinasc SMS-SP has initiated a partnership with the Center for Medical Genetics, Universidade Federal de São Paulo (CGM-Unifesp), which, perhaps, since then, taught courses are directed to their neonatologists, pediatricians, geneticists, gynecologists/obstetricians, nurses, in order to upgrade and improve the content of the theoretical and clinical, for the timely diagnosis of CAs is at birth, and by emphasizing the need for, and importance of taking notes on this analysis in DNV, and in the Sinasc, a total of 21 courses in 2020.

Other actions were developed from 2005, namely:

1 Holding seminars, individual and collective workshops, technical meetings aimed at professionals who fill in the information in DNV and for those who enter this data in Sinasc.

2 Guidance and support to hospitals, by phone, e-mail, WhatsApp, for clarification of CA coding doubts and identification of cases with complex diagnoses, counting on the collaboration of the program for improvement of mortality Information (Pro-Aim) of SMS-SP and CGM-Unifesp.

3 Preparation of Manual de Anomalias Congênitas, in partnership with CGM-Unifesp: 1st edition in 2008,[13] 2nd edition in 2012,[14] revised and expanded, containing the collection of images provided by Eclamc to facilitate diagnostic identification, available on the Sinasc website and distributed in print to hospitals, other health services, doctors, nurses and other employees of Sinasc. In 2017, it was made available in QR Codes, by chapters and in the full version.[15]

4 Preparation of the reports to hospitals related to the diagnosis of microcephaly, in partnership with other technical areas of SMS-SP, for notification of cases in Sinasc, in December 2015.[16]

5 Preparation of printed and electronic manuals (2008 and 2010) to guide the completion of the DNV and its typing in Sinasc.[17]

6 Making videos about head circumference measurement technique,[18] in 2017, and guidance of filling in the DNV and its typing in Sinasc,[19] in 2020.

7 Creation and maintenance of Sinasc page, available on the portal of the City Hall of the municipality of São Paulo, with legislation, publications and guidelines for hospitals, civil registry offices, professionals who provide home delivery assistance and other information.[20]

8 Monitoring of information through Monitora-Sinasc application, developed by the Management of Sinasc MSP in 2011. It allows both the system management and each hospital in the municipality, through login and password, to access reports that identify the fields of the DNV without filling, with ignored or inconsistent information, enabling the autonomy of the establishments to make the necessary corrections in the system.[20,21]

9 Sinasc seal, strategy implemented in the MSP in 2009, to reconcile monitoring, evaluation and incentive, in the form of annual certification given to health establishments that meet the predetermined criteria of punctuality (inclusion in the system of all births up to 15 days of the month following the birth) and completeness of the variables (from 95% to 100%).[22,23]

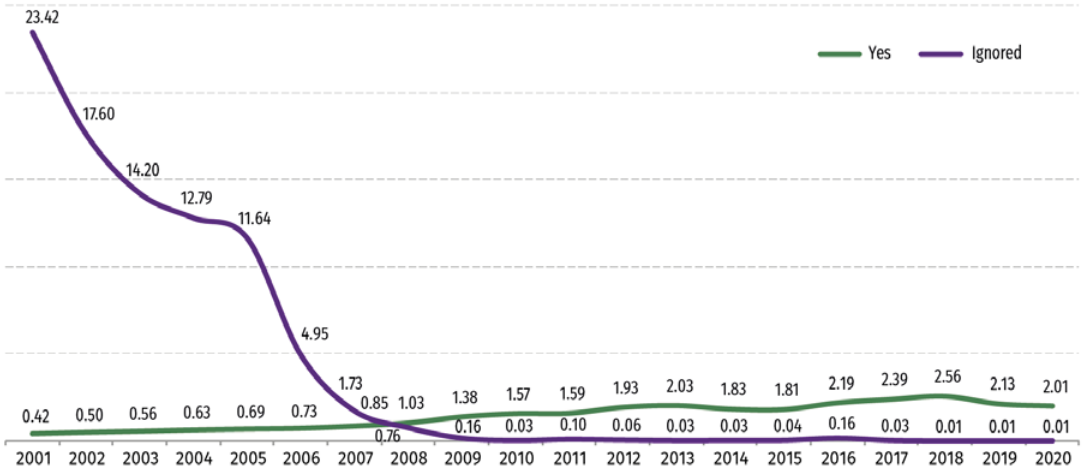
In the period from 2001 to 2020, the total LB of births occurred in the MSP and registered in Sinasc decreased by approximately 17.0% (Table 1). Regarding the "presence of CA" in the DNV, there was a reduction in ignored/absent information from 23.42% in 2001 to 0.01% in 2020, and an increase in the reporting of CA from 0.42% to 2.01% in the same period (Table 1, Graph 1).

Table 1 – Number and proportion of live births, according to information of presence of congenital anomaly and year of birth. Municipality of occurrence of the birth: São Paulo, 2001 to 2020

YEAR OF BIRTH	YES		NO		IGNORED		TOTAL NV
	N	%	N	%	N	%	
2001	830	0.42	150,030	76.16	46.128	23.42	196,988
2002	977	0.50	161,145	81.90	34.635	17.60	196,757
2003	1.098	0.56	166,827	85.24	27.791	14.20	195,716
2004	1.252	0.63	170,786	86.58	25.223	12.79	197,261
2005	1.338	0.69	170,241	87.67	22.604	11.64	194,183
2006	1.397	0.73	179,870	94.32	9.436	4.95	190,703
2007	1.612	0.85	183,991	97.42	3.270	1.73	188,873
2008	1.960	1.03	186,357	98.20	1.447	0.76	189,764
2009	2.646	1.38	188,367	98.45	310	0.16	191,323
2010	3.003	1.57	188,487	98.40	59	0.03	191,549
2011	3.085	1.59	190,916	98.32	185	0.10	194,186
2012	3.767	1.93	191,224	98.01	113	0.06	195,104
2013	3.915	2.03	188,708	97.94	54	0.03	192,677
2014	3.625	1.83	194,426	98.14	66	0.03	198,117
2015	3.586	1.81	194,786	98.15	81	0.04	198,453
2016	4.138	2.19	184,613	97.65	299	0.16	189,050
2017	4.535	2.39	185,137	97.58	62	0.03	189,734
2018	4.740	2.56	180,264	97.43	13	0.01	185,017
2019	3.778	2.13	173,841	97.87	11	0.01	177,630
2020	3.281	2.01	160,266	97.99	11	0.01	163,558

Source: Live Birth Information System, São Paulo Municipal Health Department, February 2021[32].

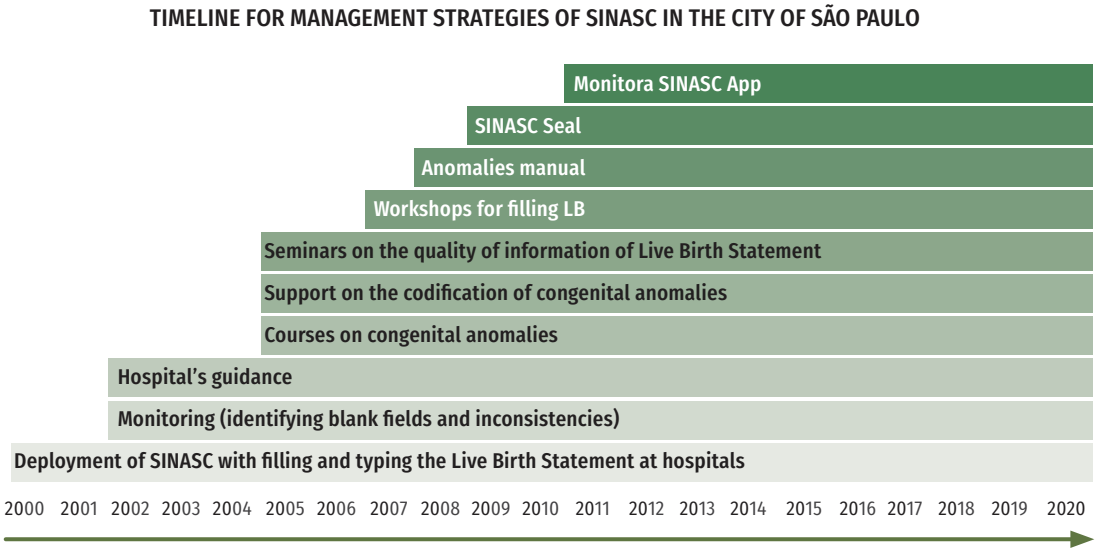
Graph 1 – Proportion of live births, according to information of the presence of congenital anomaly and year of birth. Municipality of occurrence of birth: São Paulo, 2001 to 2020



Source: Live Birth Information System, São Paulo Municipal Health Department, February 2021[32].

In the timeline (Figure 1), it is possible to follow the various strategies developed that contributed to the observed changes.

Figure 1 – Strategies adopted by the management of the Live Birth Information System in the city of São Paulo, to improve the quality of information, 2001 to 2020



Source: Live Birth Information System, São Paulo Municipal Health Department, February 2021.[32]

DISCUSSION

Recommendations, within the framework of the WHO in 1958, made obvious the need for prospective studies of CAs in different countries and that should be hospital-based in selected maternity hospitals. These discussions culminated in the realization of the first worldwide epidemiological study of CAs detected at birth. The historical publication took place in 1966, in a special supplement of the Bulletin of the World Health Organization with 127 pages. It reports the study of live and dead births with CA in 24 maternity hospitals in 16 countries, involving 421,781 newborns.[24] Brazil was represented by a Maternity Hospital in the city of São Paulo, a landmark of the Brazilian obstetric clinic and neonatology, Casa Maternal Leonor Mendes de Barros. Created in 1944 by the State Government of São Paulo and ceded to the Brazilian Legion of Assistance (LBA), the Leonor Mendes de Barros Maternity Hospital (HMLMB) was inaugurated as a maternal and childhood home, with the aim of providing care to women in need, especially pregnant and parturient women. In 1987, with the implementation of the Unified Health System (SUS), it became the own hospital of the State Health Department of São Paulo. It provides specialized care in obstetrics, gynecology and neonatology, and is one of the reference hospitals for high-risk pregnant women, being awarded and recognized by international bodies such as the WHO and the United Nations Children's Fund (UNICEF).[25] In the decades of 1950-1980, dozens of hospital-based epidemiological studies, prospective or retrospective, case-control or not, such as that of the Leonor hospital investigated CAs in newborns on all continents. Differences in the prevalence of certain CA were evident, most of the time, related to the ethnic and/or geographical stratum of the reference population. The overall prevalence of CAs was characterized as being around 2% to 3%.[26]

The actions developed by the managers of the SINASC of SMS-SP, starting from the year 2001, had as a goal to reach the notification of at least 2% of CA in the system. As seen in Table 1, Chart 1 and Figure 1, this milestone begins to be reached and maintained 10 years later.

The implementation and, above all, the maintenance of each strategy, in a work process progressively improved and expanded, was decisive to qualify the information on LB, resulting in a reduction in the number of ignored or absent and an increase in CA records. The continuous support for coding, the ongoing education process with courses aimed at improving the diagnosis and registration of congenital anomalies in DNV and Sinasc, meetings in hospitals, meeting local needs, were key parts.

The expansion of monitoring, initially carried out only by Sinasc managers, from the Monitora-Sinasc,[21,27] in 2011, it represented a milestone in the direction of the leading role of hospitals, with the possibility of checking, autonomously, inconsistencies and fields without filling for correction.

The Sinasc Seal is worth mentioning, a motivating award that has enhanced the set of actions carried out, in addition to providing visibility to health establishments that are committed to the qualified filling of the DNV and its typing in the system in a timely manner.

The continuity of actions over time provided stimulus, trust, reciprocity, strengthening of ties and greater articulation between the various sectors related to Sinasc.[28,29] A qualitative study carried out at the MSP with nurses from public and private hospitals verified that professionals identify themselves as an integral part of the Sinasc information production process, understanding the meaning of and the importance of what they do. The authors reported that the participation of nursing professionals was fundamental for the quality of records.[28]

It is worth mentioning the participation of Sinasc MSP, as a member of the Latin American network for the surveillance of congenital malformations (ReLAMC),[30] since its inception in 2016. Composed of the countries of South, Central America, the Caribbean and Mexico, it aims to strengthen surveillance and provide up-to-date and reliable CA information in Latin America. Being part of this network represents, for the municipality of São Paulo, an achievement and a commitment, increasingly, in the production and quality of data, in addition to the valuable opportunities for collaboration, growth, exchange of experiences and conducting joint studies, to better subsidize public health care policies.

However, there are challenges to be overcome to further reduce underreporting and that require new approaches, especially regarding the heterogeneity of the prevalence observed among the different maternity hospitals of the MSP. Some unfavorable and relevant aspects that interfere in obtaining information about the presence of CA concern the organization of services in their work process. One of them is the high turnover of professionals in health facilities; another, the routine established by some institutions for the filling of the DNV, often verified in the obstetric center itself, immediately after the occurrence of birth, compromising the identification of CA that can be better observed after detailed Anamnesis and other diagnostic support tests. Another issue is the lack of knowledge or even little attention on the part of some professionals regarding the need to make this information available in the medical record. Also the absence or instability of communication flow between the hospital sectors impair the capture of information. Sometimes, the annotation is present in the medical record, but there may be difficulties of understanding, both of administrative and nursing professionals, in relation to readability, or even whether or not the record relates to AC[9].

A strategy to evaluate underreporting in Sinasc can be the systematic relationship with other databases, such as those of the Mortality Information System (SIM)[31] and the Hospital Information System (SIH).

The advances obtained with the improvement of the quality of information on CA are directly related to the set of actions carried out, some quite innovative. However, one cannot lose sight of the many challenges present that require permanent actions of motivation, monitoring and improvement.

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14 THE GLOBAL BIRTH DEFECTS WEB APPLICATION (APP) FOR THE DESCRIPTION AND CODING OF CONGENITAL ANOMALIES

SUMMARY

OBJECTIVE

To present the role and functionality of the App The Global Birth Defects Description and Coding (GBDDC) application for the description and encoding of congenital anomalies.

METHODS

The application was produced by the International Committee for Congenital Anomalies Surveillance Tools, composed of members from Europe, Latin America, Africa, Asia and the USA, in response to the Zika virus epidemic in Latin America, and translated into Spanish and Portuguese.

RESULTS

The GBDDC app contains images of 98 externally visible congenital anomalies (88 major and 10 minor) and 12 syndromes (including the Congenital Zika Syndrome) or rare anomalies (such as siamese twins). For each anomaly or syndrome, the definition and code of ICD-10 are provided. The App also contains videos about newborn examination provided by WHO/TDR, and many pages of the App have additional information and links to extra resources. It can be used on mobile phones and tablets and functions on Android and Apple operating systems, and one of the important aspects of the surveillance version of the GBDDC app is to ensure data security.

CONCLUSION

The GBDDC app is designed to facilitate accurate data collection in low-resource locations and provide an introductory training tool for health professionals responsible for identifying and coding birth defects. However, it is important to highlight that it is limited to surveillance and the need for research, not being a medical or health device.

KEYWORDS

Congenital abnormalities. ICD-10. Surveillance in public health. Epidemiological surveillance.

INTRODUCTION

In the past three decades, Brazil, like many low and middle income countries (LMICs) has experienced an epidemiological transition where congenital anomalies (CAs) have risen as a leading cause of infant morbidity and mortality as infectious diseases decline.[1] In 2015, CAs were ranked as the 2nd leading cause of under-five mortality in Brazil compared to 1990 when they occupied the 5th position.[2]

Prevention, detection and treatment are the key strategies recommended by the WHO to reduce the burden of CA.[3] In all three strategies, CA surveillance has a central role. In 2010, during the World Health Assembly, the WHO passed a Birth Defect Resolution (WHA63.17) that called for the strengthening of birth defect surveillance systems globally and nationally. The recent Zika virus epidemic in Brazil and other Latin America countries that led to many babies being born with CA of the brain, eyes and neurodevelopmental sequelae (congenital Zika syndrome), has further emphasized the need to strengthen surveillance systems in Brazil and other LMICs.[4]

A critical component of the CA surveillance process requires collecting accurate CA data from hospitals and/or communities and forwarding them to the central surveillance system for validation. Unfortunately, accurate data collection (identifying, describing, coding and classifying the CA) requires expert knowledge which is often limited in low resource settings. Another important challenge for low resource settings is the ability to securely and rapidly transmit data collected from the hospital or community to the central surveillance system. One option available to health care staff at the point of care in LMICs is to use a reference guide to facilitate the description and coding of CA, either the WHO Quick Reference Handbook available in paper or electronic pdf form5 or the Latin-American Collaborative Study of Congenital Malformations (ECLAMC) electronic database.[5]

In this paper we discuss the role of the new Global Birth Defects Description and Coding (GBDDC) App in facilitating accurate data collection in low resource settings and as an introductory training tool for health professionals. The App was produced in response to the Zika virus epidemic in Latin America by the International Committee for Congenital Anomaly Surveillance Tools, comprising members from Europe, Latin America, Africa, Asia and the USA. It will be used as a training tool for the new program of congenital anomaly surveillance in Brazil.

OVERVIEW OF THE GBDDC APP

The GBDDC App contains images of 98 (88 major and 10 minor) externally visible CAs and 12 conditions which are either syndromes (including congenital Zika syndrome) or rare conditions (such as conjoined twins). For each CA or syndrome, the definition and ICD10 code with RCPCH extension (see Appendix A for a complete list of CAs included in the App) are given, and a range of illustrative photos and diagrams sourced from the WHO/ICBDSR/CDC Atlas of Birth Defects, the ECLAMC online database, and other sources. The App also contains video material on the newborn examination provided by WHO-TDR. It is designed to be used as a companion tool by a wide range of health professionals contributing to CA surveillance and research in low resource environments to guide the accurate describing and coding of CAs. The App is for surveillance and research purposes only, and is not intended to replace referral of the baby for a clinical diagnosis, or to inform care options requiring clinical input. Although a few syndromes are included in the App, in general syndrome diagnosis should be done by specialists. The GBDDC App can be used in mobile phones and tablet devices and functions in both Android and Apple operating systems.

The App exists in two versions:

- The Basic Version designed for use by persons with an interest in understanding/improving CA diagnosis or coding. This version can be used for training purposes. It does not allow for recording of data. It has been reviewed by experts and has been available for use in Apple and Google play stores since October 2019. This version is soon to be piloted in Rio Grande do Sul for congenital anomaly surveillance.
- The Surveillance Version is an extension of the basic version to allow recording of pseudonymised data for each baby. It is designed for use by surveillance and research systems. It is currently being field tested. For users with appropriate ethics permission in place, photo taking capacity may also be available.

To use either version of the App, the user must first download and register using a registration code. This process requires access to the internet. However, internet is not required for navigating the App, an important feature in facilitating the use of the App. The App has been translated into Spanish and Portugese.

The Global Birth Defects Website provides additional information about the GBDDC App, including updates and training videos.

HOW TO DOWNLOAD AND REGISTER TO USE THE APP

The GBDDC App is available for download in the Google play store and Apple store. Once you have downloaded the App, you will need to register using a registration code. The registration code determines which version of the App you will see. For the Basic Version, use the code **XJNL**.

During registration, the user is required to provide a small amount of personal data and create a pin. The user must then login using their user name and pin to be able to acess the App. The requirement of a registration code and need to login means that the images in the App can only be viewed by registered users, and provides data security to users of the surveillance version. The App allows multiple user accounts on the same device (e.g. tablet).

To get a registration code to use the Surveillance Version, users must first apply to Global Birth Defects (email:globalbirthdefects@tghn.org), in order to be issued a unique institutional code. A video about downloading and registration is available on the Global Birth Defects website (globalbirthdefects.tghn.org).

HOW TO USE THE GBDDC APP

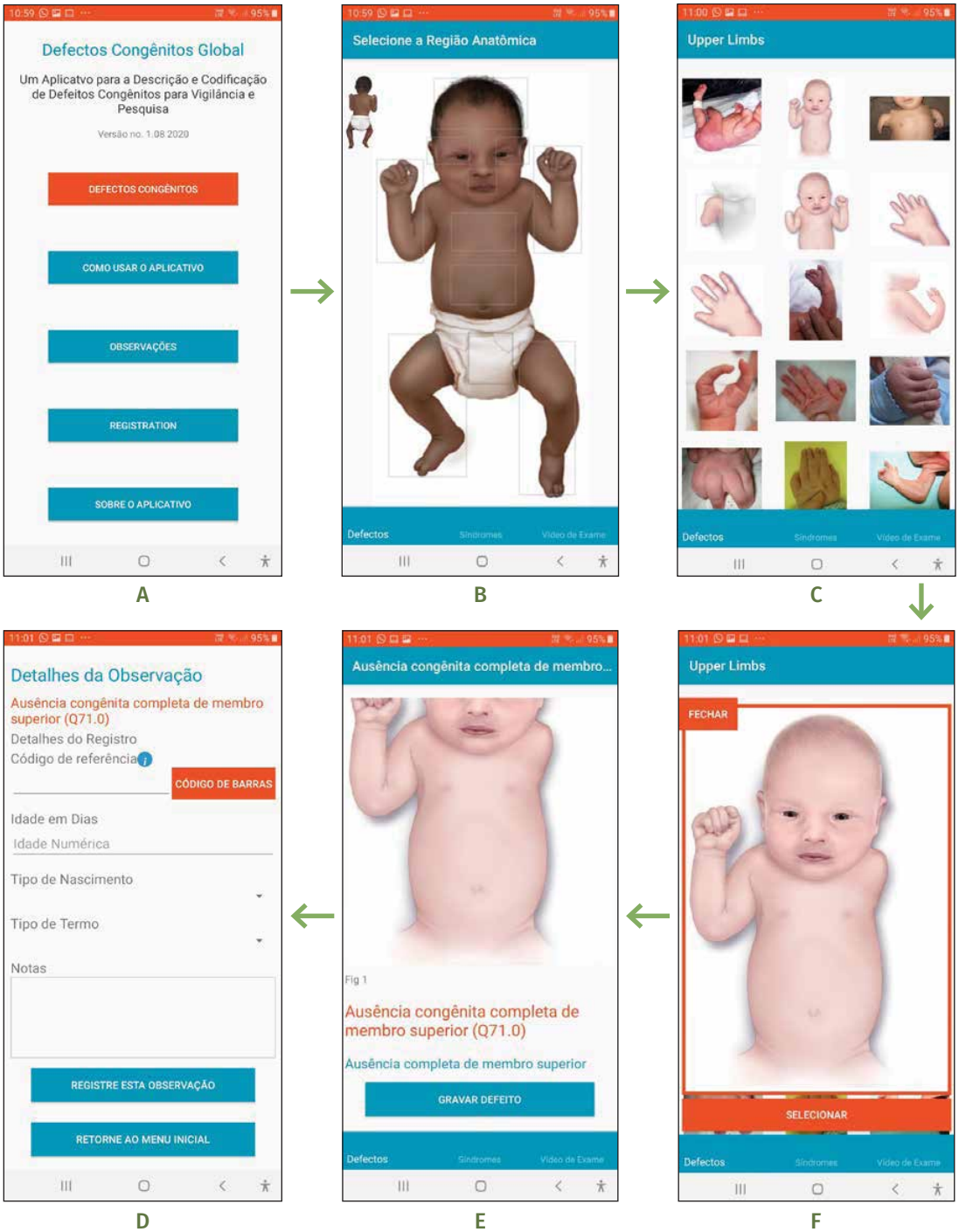
The GBDDC App is designed for use by healthcare staff or research staff who observe the baby within a few days of birth, noting major externally visible CA.

The process simply requires choosing a correct image from a series of different options. As the user taps the screen, the App enables him/her to select a region of the body, then to select among a range of images to choose the birth defect that best resembles what they observe in the patient (baby) (Figure 1).

Both the Basic and Surveillance versions can facilitate accurate identification, description and coding of the CA. Surveillance version users are able to proceed to the “Observation Details” page (Figure 1F), where they will be able to enter a small amount of diagnostic information. For each CA,the name (orange), ICD code and description (blue) are given. The basic version user can simply copy these into their note book or data entry device.

If the baby has multiple anomalies, the user will repeat the navigation pathway, until all the other anomalies have been recorded. It is important for the user to record details of the malformation observed which may not be captured in the standard description text provided in the App. Details such as position/location of the anomaly (e.g. left or right side), size/dimensions, shape and nature of membrane covering are important features that may assist in the accurate diagnosis of the anomaly by the BD specialist reviewing the data.

Figure 1 – Birth defect selection pathway (e.g. Congenital complete absence of upper limb - Q71.0)[12]



Source: adapted from Global Birth Defects Description and Coding, 2021.

DISTINGUISHING SIMILAR ANOMALIES

The App helps users to different between similar CA (Figure 2A). A dark blue link in the CA page tells the user that there are similar CAs. For example, Figure 2A distinguishes between preaxial and postaxial polydactyly. The App also helps users to distinguish and correctly record CA having subcategories with different ICD codes. For example, hypospadias is presented in the App with three different subcategories (glanular, midshaft, penoscrotal), each having a unique ICD code (Figure3 B). Only a single image of CA can be seen at a time. An orange arrow (Figure 2B) indicates to the user that there are more images to be viewed by scrolling to the right. These images could be for different subcategories of the CA (e.g. as in the case of hypospadias in Figure 2B) or for the same CA.

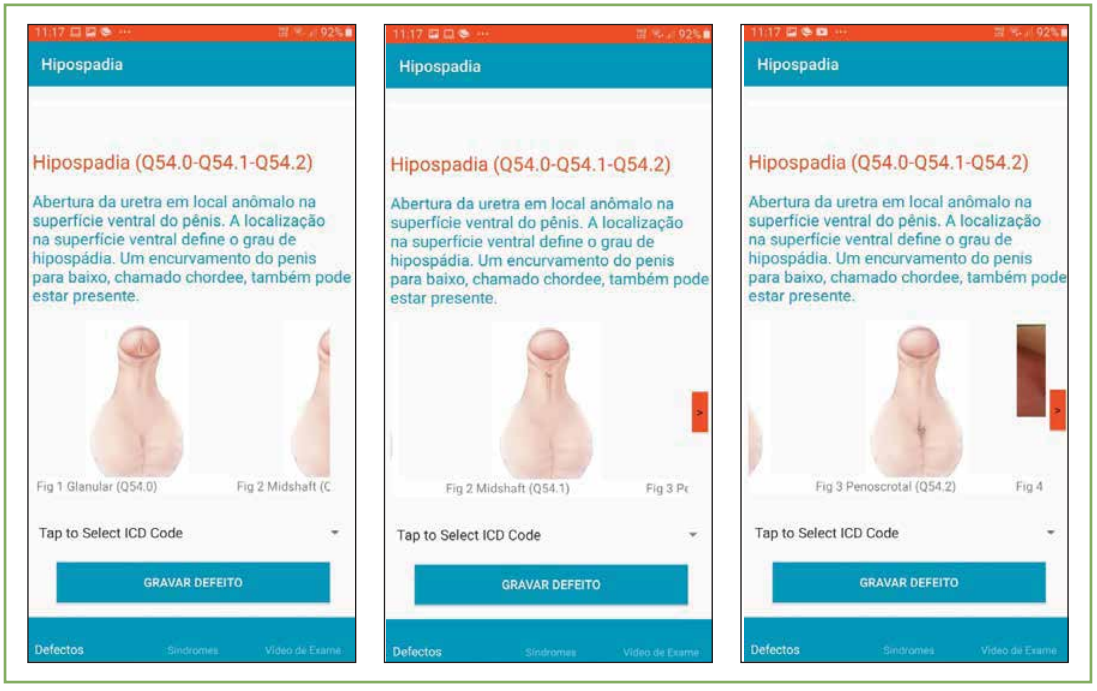
Some decisions were made regarding the accuracy with which non-expert health professionals can be expected to distinguish visually between similar CA. For example, hypospadias is given in three subcategories rather than the multiple subcategories of the ICD10 code. Skeletal dysplasias are grouped under a single ICD10 code (Q77), with a variety of photos, but it is considered that distinction between different types of skeletal dysplasia is unlikely to be accurate.

MINOR ANOMALIES

Minor anomalies, defined as those that do not have significant surgical, medical or cosmetic importance, are the most common in babies. Minor anomalies are particularly important when recording data for syndromes as they often form part of the characteristics features of a syndrome. Major anomalies on the other hand are the primary focus of surveillance systems. A few (10) of the most common minor anomalies have been included in this app to help users identify common minor anomalies seen at birth and to advise that these need not be recorded if isolated. No ICD codes are given for these minor anomalies. In the surveillance version, there is no option for the user to record data for minor anomalies, but the user can record data on a minor anomaly in the “notes” field of a major anomaly or syndrome.

Figure 2 – "Differential diagnosis" of postaxial and preaxial polydactyly of fingers (A) and subcategories of hypospadias with different ICD-10 codes (B)[12]

A



B

Source: adapted from Global Birth Defects Description and Coding, 2021.

SYNDROMES

Syndromes are recognizable patterns of congenital anomaly (major and minor, externally visible and not) which appear together in the same baby and are assumed or known to be causally related. A syndrome can have a genetic origin (e.g. Down Syndrome), or be caused by an environmental teratogen (e.g. congenital Zika syndrome). Most CA are thought to be caused by a combination of genetic and environmental factors. Syndromes, however, have a single main cause. In the GBDDC app, we include only very few of the many syndromes which exist – selected because they are relatively easily recognizable at birth or have public health significance because of their higher frequency or preventability.

The diagnosis of syndromes requires a high level of expertise, to distinguish similar conditions, or to ascribe a genetic mutation or chromosomal aberration as the cause. The App is not sufficient to diagnose syndromes with confidence, for which referral of mother and baby to a clinical specialist for diagnosis and counselling is required. However, it can help guide the user to observe and describe the baby carefully and be aware of possible causes. Some of the syndromes (e.g fetal alcohol spectrum disorder) are particularly difficult to diagnose at birth but have been included for educational purposes in terms of their public health importance.

The syndrome tab is located at the bottom of the App screen. To record data on syndromes the user follows the same pathway as previously described. Syndromes are often characterized by the presence of multiple anomalies (including minor anomalies). The user should ensure that they record all the major and minor anomalies associated with the syndrome, not just the syndrome code.

RECODING DATA FOR CONGENITAL ZIKA SYNDROME (CZS) AND MICROCEPHALY

Particular attention is given to congenital Zika syndrome (CZS) and microcephaly since the App came from a need to respond to the Zika virus epidemic. To record data for a case with CZS, the App guides the user to first record evidence of maternal Zika infection during pregnancy (maternal report and/or laboratory confirmation) and then record all the CAs present. Once the surveillance system receives those data, they can further evaluate if the case meets the criteria for a probable or confirmed CZS case.

The microcephaly page has videos on head circumference measurement and Intergrowth and WHO charts for head circumference thresholds. A “microcephaly calculator” automatically classifies babies into normal head circumference (>-2SD), microcephaly (-3SD to -2SD) and severe microcephaly (<-3SD) based on information entered on the head circumference (in cm with one decimal point), gestational age and sex of the baby (Figure 3). This calculator is available in both the basic and surveillance versions.

Figure 3 – Page showing the microcephaly severity calculator (the data entered indicates that the baby has severe microcephaly)[12]

Source: adapted from Global Birth Defects Description and Coding, 2021.

TRAINING AND SUPPORT

Many anomaly pages in the App have additional information and links to extra resources. The bottom right tab of the App contains neonatal examination videos (provided by WHO-TDR) that guide the user on how to perform a newborn examination to identify and report on CAs. More information on birth defects surveillance tools can be obtained from the Global Birth Defects site (https://globalbirthdefects.tghn.org/resources-inventory/). This website link is also available from the home page of the App under "HOW TO USE THE APP". A section of this website is dedicated to the App with supporting information, including a series of instructional videos on:

- Introducing the Basic Version of the GBDDC App https://youtu.be/wzZ5-Ambc-g
- Innovative solutions: Introducing our App https://youtu.be/Mdf7F8i7azg

- How to Download and Register for the App https://youtu.be/HcayOg7Go3s
- How to Navigate, Record and Upload Data https://youtu.be/d4LM5BLpxPQ
- Recording Data for Congenital Zika Syndrome and Microcephaly https://youtu.be/Vl-d61SeViE

DISCUSSION

The World Health Organization (WHO) defines mHealth as 'medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices'.[7] The dependence on wireless communication and mobile devices differentiates mHealth from the closely related concept of eHealth (electronic process in health) which focuses on desktop computers. We have described how one such mHealth application, the Basic version of the Global Birth Defects app, can facilitate the accurate description and coding of CAs by non-expert health professionals, either as a training tool or to be used when recording data. The surveillance version of the App which offers more data collection functionality is still undergoing field testing.

WHO has just launched a revised version of "Birth defects surveillance: quick reference handbook of selected congenital anomalies"[8] available currently in pdf or printed form. This revised handbook also includes congenital heart disease and other non-externally visible CA, as well as more extensive material on congenital infections, and it is intended that the next version of the GBDDC app will point users to these additional materials. However, the GBDDC app is mainly designed for use by non-experts conducting an external newborn examination. As the baby is referred onwards in its clinical care pathway, more information may become available from echocardiograms and other investigations which are also important to CA surveillance, and for which reporting pathways must be established.

The GBDDC app is limited to a generic surveillance and research need - it is not a medical or healthcare device. There is potential to expand the mHealth concept for congenital anomaly prevention and care in many ways, targeted at healthcare professionals as well as parents. It is important to keep each App relatively simple to use, and well targeted in its purpose and users, but a suite of mHealth applications could be envisaged. The closer the App comes to the provision of care, the greater the need for a nationally tailored app, which can explain to health professionals and/or parents where they can obtain support and resources, and which relates to national standards of care.

The GBDCC app is ready for use in future Zika outbreaks in Brazil[9] and elsewhere. It is well established that the monitoring of microcephaly requires accurate data on head circumference,[10] which can be facilitated by the head circumference training videos contained in the App, and the microcephaly calculator. The pages on congenital Zika syndrome can help raise awareness among health professionals of its various presentations at birth, and the need to record relevant details regarding exposure and clinical presentation. However, health systems should not await the results of CA surveillance to alert them to a Zika outbreak - surveillance of the *Aedes Aegypti* mosquito vector, serologic surveillance, and sentinel infection surveillance among pregnant women, should

give earlier warning. Moreover, the scientific evidence necessary to better protect pregnant women from infection is already available, and includes sanitation and water supply measures which prevent mosquito breeding grounds, other vector control methods, protective clothing and repellents, pregnancy planning, and eventually vaccination.[9] In this context, surveillance of congenital Zika syndrome and of microcephaly can evaluate the success of the overall preventive strategy, and identify high risk groups.

The proliferation of mobile phones in Brazil over the last decade has given rise to a dramatic rise in the number of mHealth technologies.[11,12] A survey in 2013 analysed 42 mHealth projects that have been undertaken in Brazil.[11] This rise in the use of mHealth technologies demands greater interoperability and uniform standards for data protection. One of the important aspects of the surveillance version of the GBDDC app is to assure data security. The pseudonymised data are collected on phones/tablets protected by a pin, and are uploaded to a secure server (and deleted from the device) as soon as possible. The data can be downloaded from the secure server (and deleted) by the data manager. This system avoids circulation of photos or information by email or even WhatsApp. The potential to create a platform where birth defect experts can securely review the information and images uploaded is being explored. The responsibility for secure use of the App lies at national level.

Other resources for birth defect surveillance can be found on the Global Birth Defects website in the resources inventory: https://globalbirthdefects.tghn.org/resources-inventory/. Here can be found links to resources regarding diagnosis and coding of CAs (e.g. the International Classification of Disease (ICD) v10. Chapter XV[11] with extra RCPCH digit, ECLAMC database, the European Surveillance of Congenital Anomalies (EUROCAT) guides for defining and coding CAs, guides to genetic syndrome diagnosis), manuals/softwares for the development of congenital anomaly surveillance programs (e.g. the WHO Birth Defects Surveillance manual designed to assist with the local development of CA surveillance systems, the ICBDR PreSurv software tools designed for the Prevention and Surveillance of birth defects), public health tools for CAs (e.g. information about disease burden and prevention of CA), teratogen information systems, information for parents, and resources for care of those affected by CAs.

The Zika epidemic shone a spotlight on many issues relating to congenital anomalies which had often been obscured. The need for accurate recording and monitoring of birth defects is one of these, and is important to making progress in preventing birth defects, and improving the care and lives of children with CA and their families.

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APPENDIX – LIST OF ANOMALIES AND SYNDROMES INCLUDED IN THE GLOBAL BIRTH DEFECTS APP DEFECTS

BODY REGION	ANOMALY NAME	CODE ICD- 10 + RCPCH
Head	Anencephaly	Q00.00
	Craniorachischisis	Q00.1
	Iniencephaly	Q00.2
	Frontal Encephalocele	Q01.0
	Nasofrontal Encephalocele	Q01.1
	Occipital Encephalocele	Q01.2
	Parietal Encephalocele	Q01.80
	Orbital Encephalocele	Q01.81
	Nasal Encephalocele	Q01.82
	Congenital Aplasia Cutis	Q84.80
	Congenital Microcephaly	Q02
	Congenital Hydrocephalus	Q03.9
	Holoprosencephaly	Q04.2
	Abnormal Shape of the Head at Birth*	
	Craniosynostosis	Q75.0
	Others	
Neck and Back	Cervical Spina Bifida with Hydrocephalus	Q05.0
	Cervical Spina Bifida without Hydrocephalus	Q05.5
	Thoracic Spina Bifida with Hydrocephalus	Q05.1
	Thoracic Spina Bifida without Hydrocephalus	Q05.6
	Lumbar Spina Bifida with Hydrocephalus	Q05.2
	Thoracic Spina Bifida without Hydrocephalus	Q05.7
	Sacral Spina Bifida with Hydrocephalus	Q05.3
	Sacral Spina Bifida without Hydrocephalus	Q05.8
	Caudal Regression	Q76.41
	Others	

To be continue

Continuation

BODY REGION	ANOMALY NAME	CODE ICD- 10 + RCPCH
Mouth and Nose	Cleft Palate	Q35
	Unilateral Cleft Lip	Q36.9
	Bilateral Cleft Lip	Q36.0
	Median Cleft Lip with or without Cleft Palate	Q36.1
	Cleft Palate with Bilateral Cleft Lip	Q37.8
	Cleft Palate with Unilateral Cleft Lip	Q37.9
	Pierre Robin Sequence	Q87.08
	Hemifacial Microsomy	Q67.4
	Agenesis/Hypoplasia of the Nose	Q30.1
	Nose with cleft, notch or fissure	Q30.2
	Other	
Eyes and Ears	Anophthalmia	Q11.1
	Microphthalmia	Q11.2
	Congenital Cataract	Q12.0
	Iris Coloboma	Q13.0
	Cryptophthalmia	Q11.2
	Eyelid Malformation*	
	Aniridia	Q13.1
	Epibulbar Dermoid	D31.9
	Anotia	Q16.0
	Microtia	Q17.2
	Others	
Chest	Cardiac Ectopia	Q24.8
	Poland sequence	Q79.82
	Nipple Accessory*	
	Others	
Abdomen	Gastroschisis	Q79.3
	Exonphalia (Omphalocele)	Q79.2
	Sequence Plum Belly	Q79.4
	Other Congenital Malformations of the Abdominal Wall	Q79.5
	Umbilical Hernia*	
	Others	
Anal	Anal Atresia with Fistula	Q42.2
	Anal Atresia without Fistula	Q42.3
	Others	

To be continue

Continuation

BODY REGION	ANOMALY NAME	CODE ICD- 10 + RCPCH
Genitourinary	Cloacal Extrophy	Q64.10
	Exstrophy of the bladder	Q64.1
	Hypospadias	Q54.0, Q54.1, Q54.2
	Indeterminate Sex	Q56.4
	Unilateral Cryptorchidism*	
	Bilateral Cryptorchidism*	
	Hydrocele*	
	Inguinal hernia*	
	Others	
Lower Limb	Arthrogryposis	Q74.3
	Congenital Clubfoot	Q66.0
	Pterygium of Joints	Q74.8
	Syndactyly, fused toes	Q70.2
	Syndactyly, Winged Toes	Q70.3
	Sinpolidactyly/Polysindactyly (Toes)	Q70.4
	Syndactyly of the 2nd and 3rd Fingers*	
	Split Foot	Q72.7
	Preaxial Polydactyly (Toes)	Q69.20
	Postaxial Polydactyly (Toes)	Q69.22
	Congenital Constriction Bands	Q79.80
	Sirenomelia	Q87.24
	Congenital Dislocation of the Knee	Q68.20
	Congenital Overgrowth of Limbs	Q74.81
	Congenital Dislocation of the Hip (Unilateral)	Q65.0
	Congenital Dislocation of the Hip (Bilateral)	Q65.1
	Congenital Complete Absence of Lower Limb	Q72.0
	Lower Limb Phocomelia	Q72.1
	Congenital Absence of the Leg and Foot	Q72.2
	Congenital Absence of Feet and Toes	Q72.3
	Congenital Absence or Hypoplasia of the Toe(s) with the Rest of the Foot Intact	Q72.30
	Absence or Hypoplasia of the First (Large) Finger of the Foot with Other Digits Present	Q72.31
	Defect of Longitudinal Reduction of the Femur	Q72.4
	Defect of Longitudinal Reduction of the Tibia	Q72.25
	Macrodactyly (Fingers)	Q74.04
	Others	

To be continue

Conclusion

BODY REGION	ANOMALY NAME	CODE ICD- 10 + RCPCH
Upper Limb	Arthrogryposis	Q74.3
	Congenital Complete Absence of the Upper Limb	Q71.0
	Upper Limb Phocomelia	Q71.1
	Congenital Absence of the Forearm and Hand	Q71.2
	Congenital Absence of Hand and Finger(s)	Q71.3
	Congenital Absence of Fingers	Q71.30
	Absence or Hypoplasia of the Thumb	Q71.31
	Radio Longitudinal Reduction Defect	Q71.4
	Split Hand	Q71.6
	Preaxial Polydactyly (Fingers)	Q69.10
	Postaxial Polydactyly (Fingers)	Q69.02
	Syndactyly, Fused Fingers (with Synostosis)	Q70.0
	Syndactyly, Winged Fingers (without Synostosis)	Q70.1
	Sinpolidactyly/Polysindactyly (Fingers)	Q70.4
	Macrodactyly (Fingers)	Q74.04
	Pterygium of Joints	Q74.8
	Congenital Constriction Bands	Q79.80
	Others	
Syndromes	Trisomy 21 (Down Syndrome)	Q90
	Trisomy 18 (Edwards Syndrome)	Q91.3
	Trisomy 13 (Patau Syndrome)	Q91.7
	Congenital Zika Syndrome	P35
	Congenital Zika Syndrome – Suspected Maternal Zika Virus Infection	Z20.8
	Congenital Zika Syndrome – Laboratory-confirmed Maternal Zika Virus Infection	U06.9
	Congenital Rubella Syndrome	P35.0
	Skeletal Dysplasia	Q77
	Other Maternal Infections (Congenital Cytomegalovirus, Congenital Toxoplasmosis, Congenital Syphilis)	(A50.9, P35.1, P37.1)
	Conjoined Twins	Q89.4
	Acephaly Acardia	P02.3
	Fetal Alcohol Syndrome or Spectrum Disorder	Q86.0
	Congenital Skin Diseases	
	Other Syndromes	

Source: authors.
Note: *Minor anomalies.

15

WEB APPLICATION (APP) OF FREE ACCESS FOR MONITORING CONGENITAL ANOMALIES: THE CASE OF RIO GRANDE DO SUL

SUMMARY

OBJECTIVE

To present a web application that integrates important epidemiological surveillance methods.

METHODS

The application was developed in the language **R** Core Team (2019) under the RStudio interface. The algorithm implemented for building the application uses of the Shiny package. Cases of congenital anomalies (CAs) occurred in the years 2010 to 2019 in the state of Rio Grande do Sul (RS) were considered. The information on the CAs and the number of live births (LBs) in the RS were obtained from the Live Birth Information System (Sinasc).

RESULTS

Among the features of the application, we highlight the generation of maps that allow the investigation of the geographical variation of CA cases observed over time, Moran spatial autocorrelation index, methods of detection of space-time conglomerates through Scan statistics, as well as several other charts, tables and descriptive statistics.

CONCLUSION

The application presented represents a tool for the surveillance of CA that allows spatial visualizations of cases, identification of spatial and spatio-temporal patterns of CAs occurrences and clusters. This tool makes it possible to inform health managers and professionals about the geographical and temporal characteristics of the prevalence of CAs, in addition to collaborating in the planning of specific prevention actions.

KEYWORDS

Congenital abnormalities. Surveillance in public health. Epidemiological surveillance.

INTRODUCTION

Congenital anomalies (CAs) are structural or functional abnormalities that occur sporadically or hereditarily and have prenatal origin. Most of the CAs cause serious health effects, significantly impacting not only the affected individuals and their families, but also the health systems and society.[1,2] In Brazil, the improvement in economic and health indicators in the 1980s led to a reduction in infant mortality rates due to perinatal causes, respiratory conditions and other infections. In contrast, mortality from CA has remained stable over the years; today, it is the second leading cause of infant mortality in Brazil.[3,4] Surveillance systems in CA are important for describing the prevalence and frequency changes of these conditions over time, allowing the establishment of primary prevention programs, systematic screening of newborns, diagnosis and referral of children to specialized health centers.[5,6] Ultimately, the continuous and systematic monitoring of Chas carried out through surveillance systems makes it possible to identify geographic clusters for these conditions.[7]

A geographic cluster of a CA is defined as the occurrence of a greater number of cases than expected for a given geographic area and for a certain period of time.[7] The identification of clusters enables the detection of CA outbreaks and the development of intervention strategies for their prevention, since many CA can be avoided through vaccination, food supplementation and prenatal care.[2,7] In addition, the detection of clusters allows the identification of environmental and/or genetic factors that may be associated with the occurrence of CA.[8] Thus, from the investigation of the pattern of geographical and temporal distribution of a cluster identified, it is possible to determine associated risk factors and generate hypotheses about the causes that led to the increase in the occurrence of this condition in a certain interval of time and space.[7,9]

Despite the importance of epidemiological surveillance systems in CAs, the tools to carry it out may be inaccessible to a large number of researchers and health managers who do not have programming skills or time disposition to use the software that aggregates spatial and spatio-temporal information in the analysis of these data. In this sense, the development of a tool for visualization and analysis of this type of data makes it possible to inform managers and health professionals about the spatial and spatio-temporal characteristics of CAs, so that decision-making and the formulation of public policies can be carried out in an accessible and agile way.

This work aims to present a web application developed in Shiny,[10] which integrates important methods of epidemiological surveillance: maps that allow the investigation of the geographical variation of CAs cases observed over time, Moran's spatial autocorrelation index,[11] methods of detecting space-time conglomerates through Scan statistics,[12] in addition to various other charts, tables and descriptive statistics. In this study, cases of CA occurred in the years 2010 to 2019 in the state of Rio Grande do Sul (RS) were considered. The application allows the interaction between the user and the content to be presented, in which it is possible to create different views, choose different filters, such as regions, municipalities or the variable to be analyzed.

METHODS

The application was developed in the **R** Core Team (2019) language[13] under the RStudio interface.[14] The **R** language it is available in open and free source, available for Windows, GNU/Linux and MacOS, and is known for providing a collaborative environment in which users can easily access the installation of community-developed packages.

The algorithm implemented for building the application makes use of the Shiny package,10 that allows you to develop web applications without the need for prior knowledge of programming languages used in the development of this type of tool. For the application, two files are required: a user interface file **ui.r**, responsible for the structure, appearance and indication of choice of filters, and a server file **server.r**, which contains the objects **R** and how they are presented.[15]

In addition to Shiny, it should be noted, among the main packages used in the development of the tool presented, ggplot2,[16] for making charts, the leaflet[17] and plotly[18], which allow the construction of interactive maps and charts, respectively, the spdep,[19] used in spatial analysis, and scanstatistics[20] for the calculation of Scan statistics. In addition to these, Chart 1 lists the other packages used for the production of the application.

Chart 1 – List of packages used in the creation of applications

PACKAGE	DESCRIPTION
shiny[10]	Creation of interactive web applications in R.
shinydashboard[21]	Changing themes and visual aspects of Shiny apps.
shinydashboardPlus[22]	Additional themes and visuals.
DT[23]	Creation of interactive tables in HTML.
leaflet[17]	Creation and customization of interactive maps.
tidyverse[24]	Loads several packages useful for database import, manipulation and analysis.
ggplot2[16]	Creation of charts.
plotly[18]	Creation of interactive web charts via plotly.js JavaScript library or from charts from the ggplot2 package.
ps[25]	Control of all system processes.
sf[26]	Tools for working with spatial data.
spdep[27]	Calculation of neighborhood matrices, Moran global index, among others.
kableExtra[28]	Creation and customization of tables.
viridis[29]	Gradient color palette options.
hrbrthemes[30]	Compilation of additional themes to the ggplot2 package.
ggbeeswarm[31]	Methods of creating categorical scatter plots.
scanstatistics[20]	Detection of clusters using Scan statistics and with the implementation of Monte Carlo test for hypothesis testing.
INLA[32]	Created to perform Bayesian inference, this package has several functions that assist in spatial analysis.
here[33]	Builds paths to your project files.

Source: authors.

The information on the CAs and the number of live births (LBs) in the RS were obtained from the Live Birth Information System (Sinasc),[34] in the period from 2010 to 2019, with the cases registered by the municipality of residence of the mother and according to the International Statistical Classification of Diseases and Related Health Problems (ICD) 10 (ICD-10).[35] To facilitate the interpretation of the results and for the reason that some types of anomalies have a very small number of cases, we chose to group similar CAs in the analysis of the data. The different ICDs were grouped according to Chart 2. For the analysis of this type of data, area data methodologies are used,[36] since the information on live births and cases of CAs are aggregated by municipality. Because it is aggregated data, a lot of caution is required when interpreting the results found, since it is possible to observe a case of ecological bias,[37] that occurs when the process of spatial aggregation causes the loss of information, leading to misinterpretations, preventing the correct identification of some parameters of interest at the individual level.

Chart 2 – List of ICDs associated with each of the anomaly groups[49]

GRUPO DE ANOMALÍAS	CIE(S)
Congenital heart disease	Q20, Q21, Q22, Q23, Q24, Q25, Q26, Q27, Q28
Abdominal wall defects	Q79.2 and Q79.3
Limb reduction defects/clubfoot/ arthrogryposis/polydactyly	Q66, Q69, Q71, Q72, Q73, Q74.3
Neural tube defects	Q00.0, Q00.1, Q00.2, Q01, Q05
Orofacial clefts	Q35, Q36, Q37
Hypospadias	Q54
Microcephaly	Q02
Undefined sex	Q56
Down Syndrome	Q90

Source: adapted from Cardoso-dos-Santos *et al.* (2021).[49]

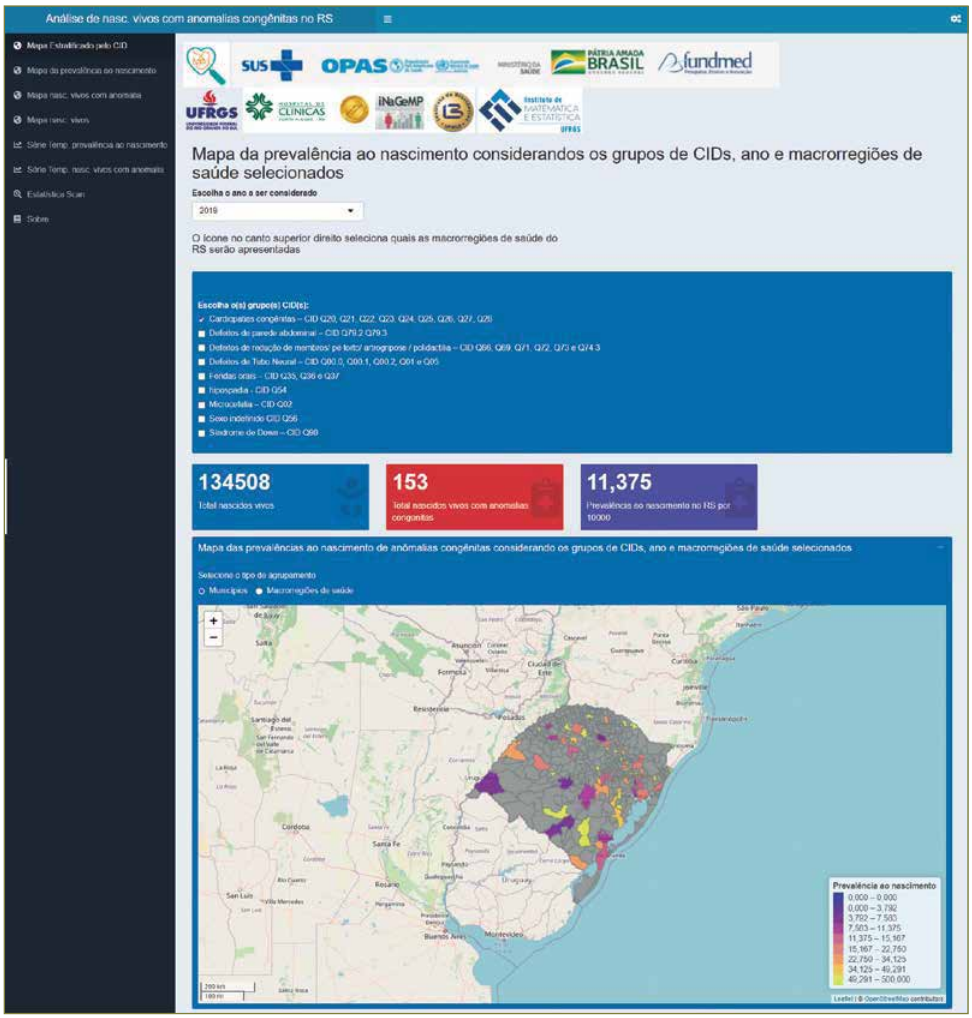
In addition to the division by municipalities, the territory of RS is divided into seven health macro-regions: Midwest, Metropolitan, Missionary, North, Sierra, South and valleys. The division into macro-regions is an important form of planning of the hospital care network and diagnostic support, so that each Health Region has its reference hospital with the capacity to attend the most complex cases,[38] assisting in the management of resources throughout the state. Thus, these regions were also considered in the application.

This project was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (Caae 30886520.9.1001.5327) and by the National Research Ethics Commission (Conep).

APP FEATURES

The information that can be obtained in the use of the application are the prevalence at birth of CAs per 10 thousand births, total number of births and number of births with some anomaly according to the municipality of residence of the mother. The main function of the tool is to provide this information through maps, historical series, density charts, tables (which are available for download), among other options, as can be seen in Figure 1, which presents the home screen of the application. All maps and charts are Interactive, which allows the user to identify which values and municipalities refer to the different observations. To do this, it is necessary to position the mouse cursor at a certain point or region in the charts presented. By clicking on the tabs, there is also the possibility to define which ICD groups will be considered in the analyses.

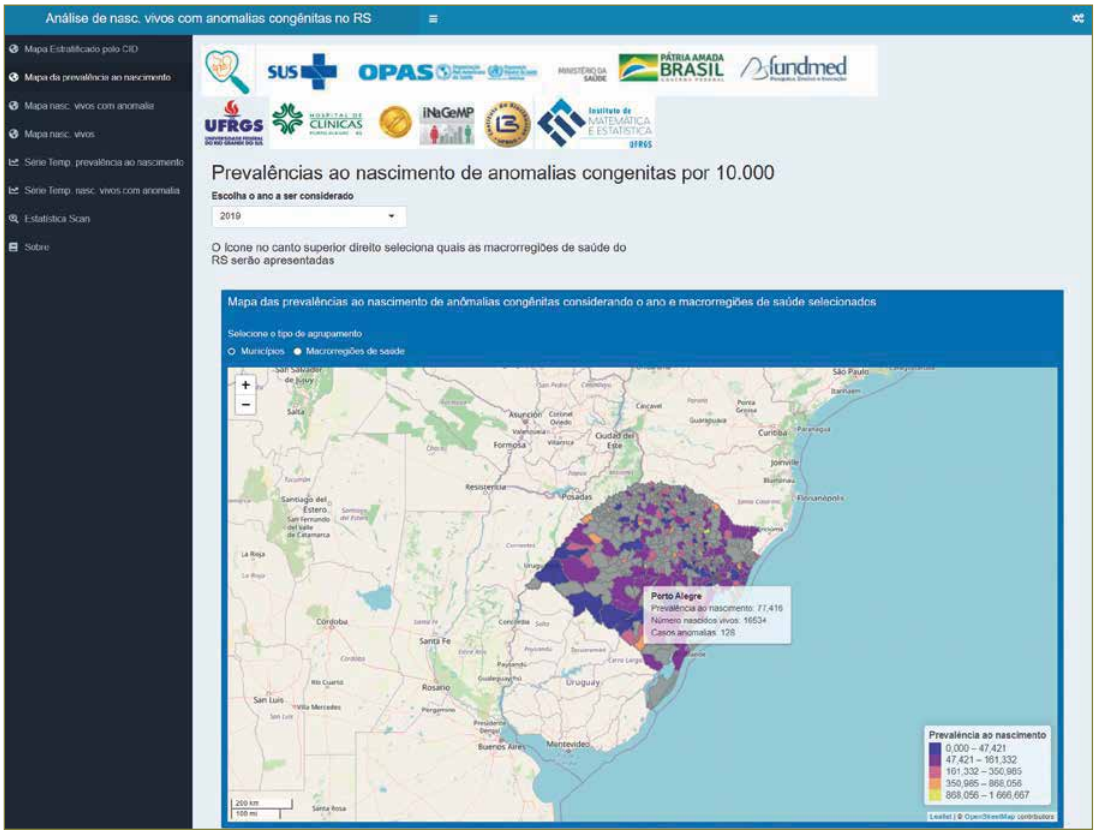
Figure 1 – Image of the tab of the application "Map stratified by ICD"[50]



Source: authors.

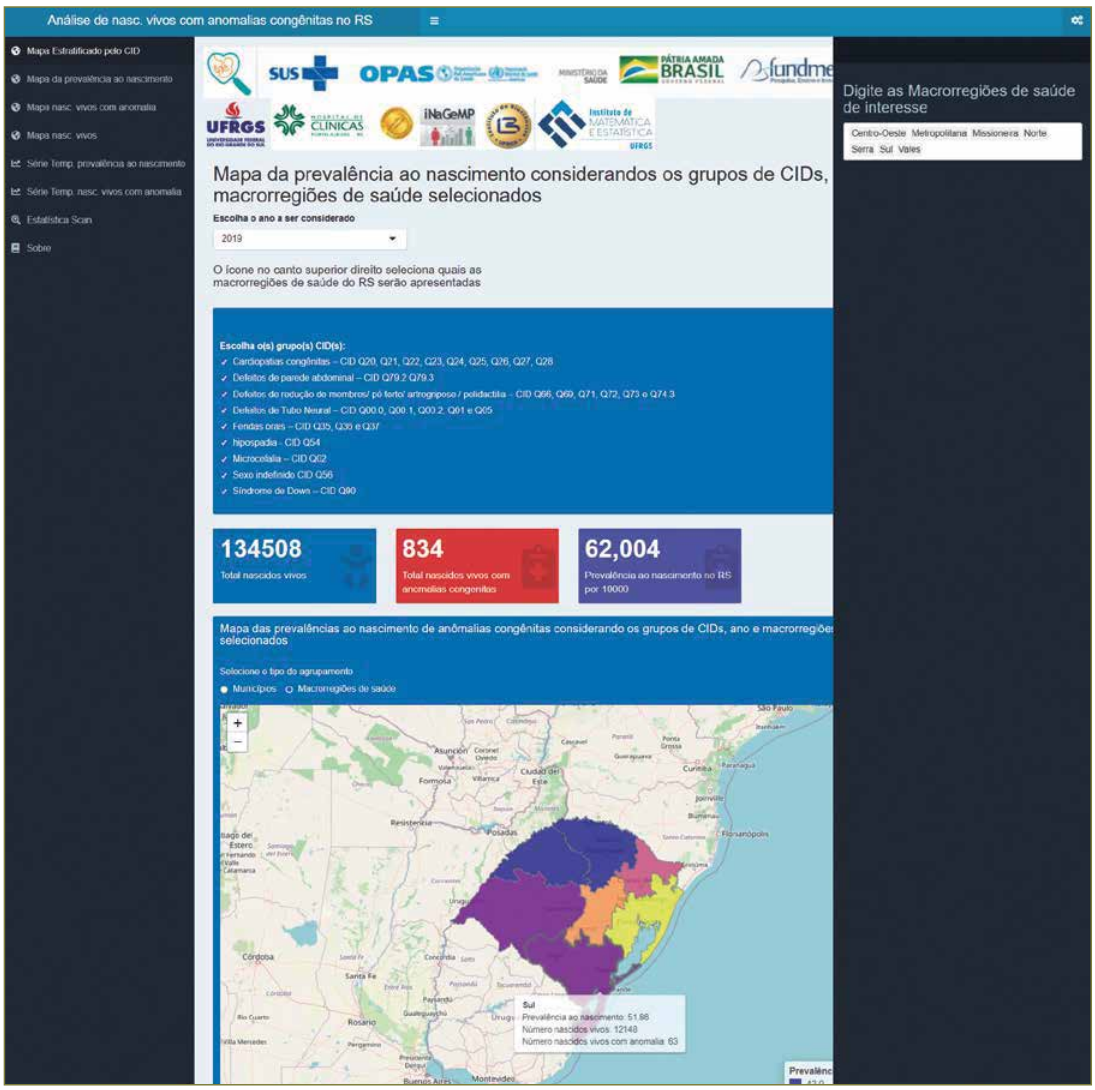
Figure 2 shows the map of the RS with the prevalence at birth of CAs by municipality, in which the regions are delimited by polygons, and the different levels of prevalence are represented by different colors, and the gray color refers to those municipalities in which there were no records of births with CA. In addition, the option to view the map according to the health macro-regions is available (Figure 3). In these maps, there is the possibility of select the groups of ICD of interest. The value of the Global Moran test I is also provided,[11] together with a map indicating the result of this test locally, through the Local Indicators of Spatial Association (LISA),[39] in which it is possible to identify areas that are similar to their neighbors, as well as hotspots, that they indicate that a given region has an expected value different from the areas around it. In the “Scan Statistics" tab, a method for identifying active spatial conglomerates is implemented. This statistic allows the spatio-temporal monitoring of the number of cases of certain groups of anomalies. Both the scan statistic and Moran's Index I will be detailed in the next sections.

Figure 2 – Image from the tab of the application "Map of prevalence at birth". In this tab, the prevalence of CAs is presented, considering all groups of anomalies[50]



Source: authors.

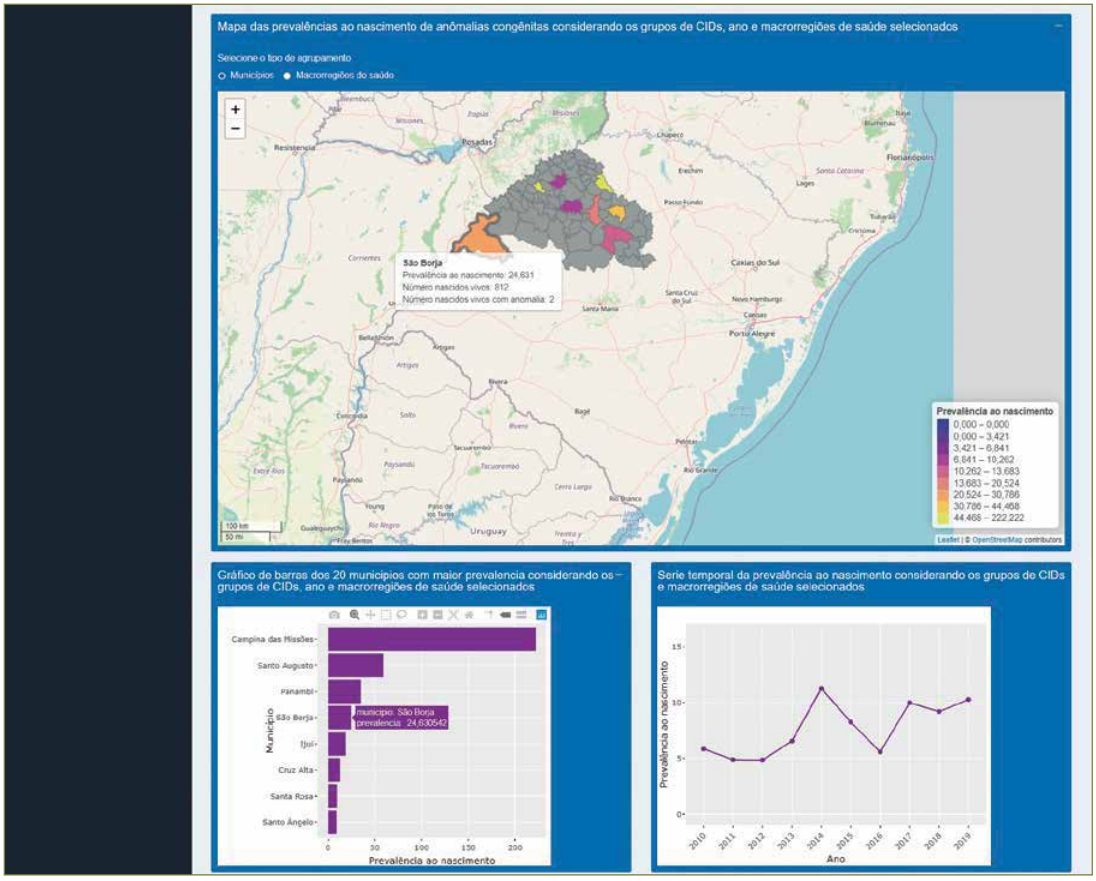
Figure 3 – Tab of the application "Map stratified by the ICD", in which are selected all groups of anomalies and all macro-regions of health. The grouping option chosen is health macro regions[50]



Source: authors.

In addition, the user can select the year and which health regions will have their data presented. Figure 4 shows an example of this type of selection, in which the year chosen is 2019, the ICD group refers to congenital heart disease and only the missionary health macro-region is selected. It is possible to observe that only the prevalence of the municipalities of this macro-region are presented on the map and that the bar charts of the 20 municipalities with the highest prevalence only contain cities in the mission region, an effect that occurs in all other charts and tables in this tab.

Figure 4 – Tab of the application "Map stratified by ICD" Congenital heart disease is the anomaly group selected, the grouping option chosen is municipalities, and the only selected health macro-region is the Missioneira[50]



Source: authors.

MORAN INDEX

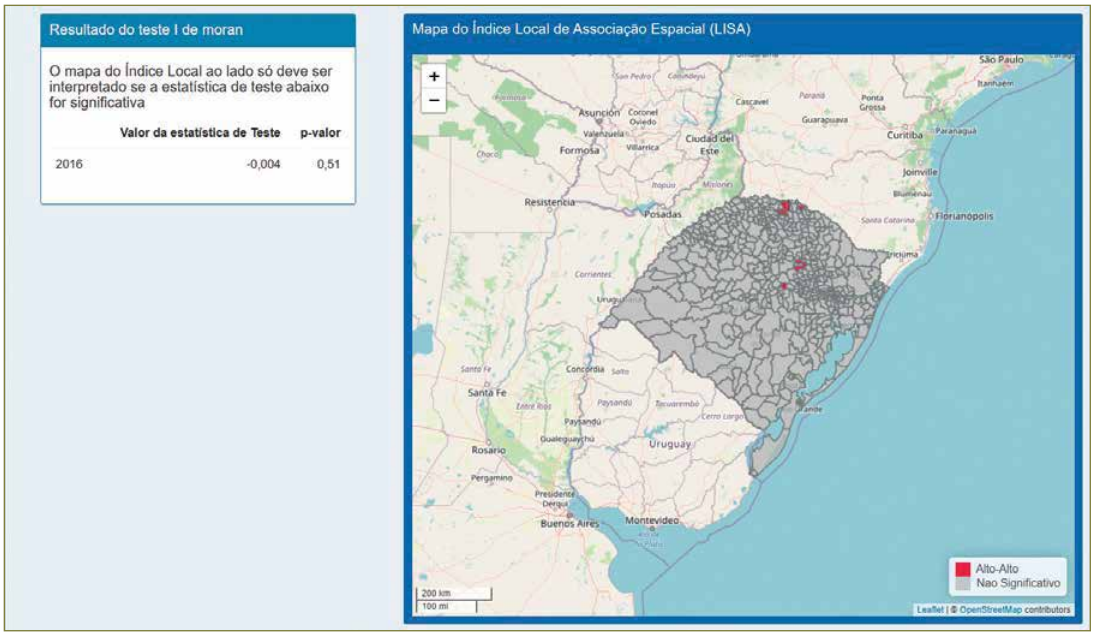
One way to evaluate spatial association is through the Moran spatial autocorrelation index.[40] In the application, the use of this statistic aimed to measure the global spatial autocorrelation between the municipalities of RS according to the prevalence of CAs. The Moran Index can be calculated as follows:

$$I = \frac{n}{\sum_{i \neq j} w_{ij}} \left[\frac{\sum_{i \neq j} w_{ij}(y_i - \bar{y})(y_j - \bar{y})}{\sum_i (y_i - \bar{y})^2} \right], i, j \in \{1, \ldots, n\}$$

in which y_i is the prevalence of CAs in the municipality *i*, $\bar{y}$ is the average prevalence, w_{ij} is the spatial weight between regions *i* and *j*, represented through the neighborhood matrix, which indicates whether two municipalities are neighbors or not, and *n* it is the number of regions considered. To test the null hypothesis that there is no spatial dependence between regions, a Monte Carlo test is employed.[41]

A positive autocorrelation indicates that neighboring municipalities tend to present similar behaviors regarding the prevalence of CAs, while a negative value of this statistic suggests that neighboring regions tend to be different. The test statistic for the evaluation of the existence of spatial autocorrelation, together with The Associated p-value, is available in the tab called "prevalence map at birth", as can be seen in Figure 5, in which the value of the Moran Global Index and the map indicating the areas with the LISA significant for the year 2016.

Figure 5 – Tab of the application "Map of prevalence at birth", with the result of the Moran Global Index test and the map of the LISA[50]



Source: authors.

Rejecting the hypothesis of absence of spatial autocorrelation, that is, if the estimated Moran Index is significantly different from zero, it is of interest to know which municipalities are spatially associated. Thus, the local indicator of spatial association (LISA)[39] it arises as a complement to the Global Index, from which it is possible to identify the correlation of each municipality with its respective neighbors, in which a municipality classified with "high-high" has an above-average prevalence and its neighbors similarly. Further details on the interpretation of the LISA can be found in Anselin.[39]

SCAN STATISTICS

For the detection of spatio-temporal conglomerates, there are two distinct approaches in the literature: retrospective and prospective.[42,43] In the prospective approach, the analysis is repeated periodically, with the aim of monitoring the number of cases of a particular disease. With each new data collected, the analysis is redone, and its interest is to detect "living" conglomerates, that is, their scanning is aimed only at detecting conglomerates that have not ceased to occur by the end date of the studied period. In the retrospective approach, the analysis is done only once, in a

fixed space and period. In this case, the interest is to detect historical or current conglomerates, aiming to understand the characteristics of a particular disease.

Several methods of prospective spatio-temporal surveillance are proposed in the literature. For Point Data Analysis, Rogerson[44] proposed the use of Knox statistics; Asunción and Correa[45] proposed the method of Shiyayev Roberts. For area data analysis and point data analysis, Kulldorff[12] proposes the use of prospective scan statistics, a statistical method to detect active or emerging geographic clusters. The generated cluster will be a group of neighboring municipalities where currently the prevalence is higher than the expected value. Such a method is commonly used for prospective surveillance of conglomerates, as it makes few assumptions about the time, geographical location and size of the outbreak. The only parameter specified by the user is the maximum population size of the cluster.

For the calculation of the scan statistic, it is necessary to specify the neighborhood structure that will be used in the analysis. Among the various forms available in the area data literature, we opted for the neighborhood structure based on spatial contiguity,[46] that is, the neighborhood matrix has value 1 when two areas divide border, and zero, otherwise. It is important to highlight that the municipality of Pinto Bandeira achieved its independence from the municipality of Bento Gonçalves only in 2013. Thus, since it is working with area data, it is not possible to identify the births that would be from the Pinto Bandeira region between the years of 2010 and 2012, so it was decided to work with the two municipalities in an aggregate form.

To find spatio-temporal cluster, the scanning method is used, generating several candidate regions to. For each candidate A, the log-likelihood ratio is calculated and the test statistic S is defined as the maximum log-likelihood ratio under all candidate regions. To obtain the p-value, the hypothesis test via the Monte Carlo method is used, which reproduces the analysis for a large number of repetitions of the original dataset under the null hypothesis of complete spatial randomness, conditioned on the total number of cases.

$$S = \frac{L(A)}{L_0} = \left\{\frac{L(A)}{L_0}\right\}$$

L(A) it is the maximum likelihood for the region *A*,
L_0 it is the maximum likelihood under the null hypothesis.

I.e Z_A the number of cases of CAs from Region A, assuming that Z_A ~ Poisson (μ_A), then the likelihood ratio can be written as (ref):

$$\frac{L(A)}{L_0} = \left\{\frac{Z_A}{\mu_A}\right\}^{Z_A} \left\{\frac{T - Z_A}{T - \mu_A}\right\}^{T - Z_A}$$

μ_A is the number of cases expected under the null hypothesis,
T is the total number of cases of CA.

The scan statistic used in the application was proposed by Neill[47] as an improvement for the detection of emerging clusters. In the above method, longer active clusters in the time had greater weight, causing greater slowness in the detection of new emerging clusters. The approach proposed by Neill improves the detection of clusters while keeping the number of false positives low.

RESULTS AND DISCUSSION

The observed prevalence of CAs of a ICD group in a municipality is defined as the ratio of the number of cases of CAs of this ICD group to the number of births in that municipality. It is important to highlight, however, that this estimate has great variance if the expected number of cases or the size of the population are small.

Therefore, the highest prevalence values tend to be observed in areas with small populations. Therefore, the greatest fluctuations in prevalence estimates, in general, will not be associated with the actual variation of the CAs, but with random fluctuations. In addition, the calculation of this ratio considers that the prevalence of the municipalities is independent, but in some cases, an unknown part of this observed variation in prevalence rates may be caused by unobserved, geographically dependent factors. Therefore, it is important to be cautious in the interpretation of the prevalence observed in the municipalities of RS.[46,48]

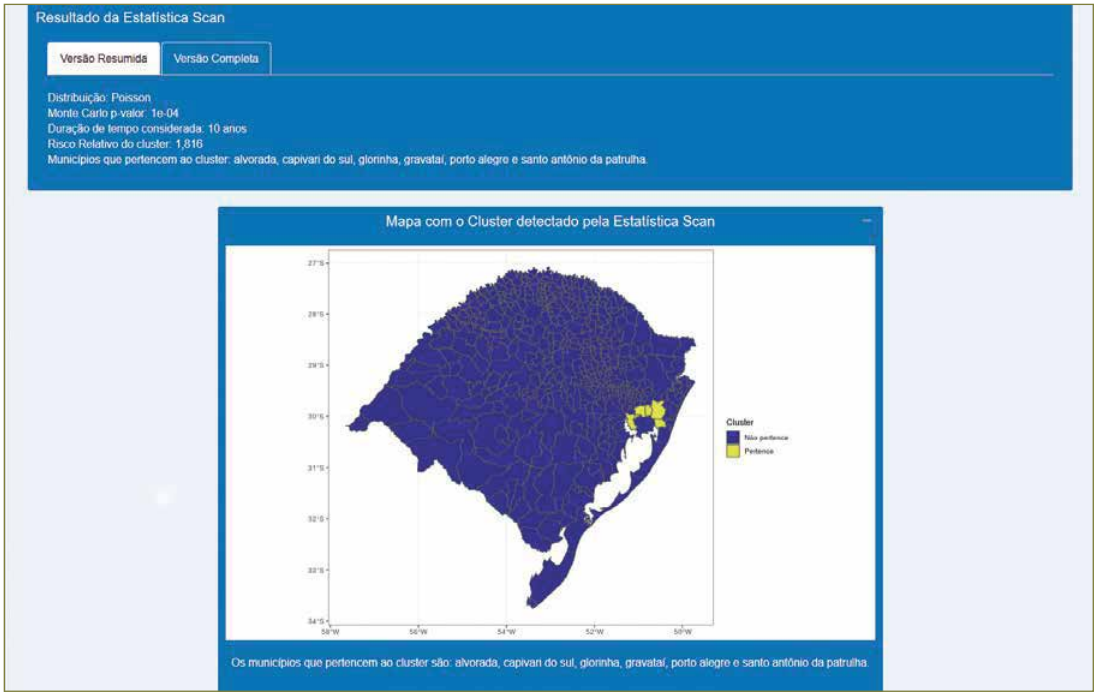
As highlighted in the features section of the application, you can choose several options among the filters. For example, the results will be displayed considering only cases of congenital heart disease in the year 2019 and in all health macro-regions.

It can be noted from Figure 1 that many municipalities have prevalence equal to zero. This is due to the fact that these municipalities have a small population and CAs are generally rare diseases. In this context, the municipality of Chapada, which recorded a prevalence of 108.69 cases every 10 thousand births, presents only one case of congenital heart disease among 92 births. This value is inconsistent, because in other years, the municipality did not register any case of this CA. One way around this problem is to use Bayesian hierarchical models. These methods, in addition to smoothing the prevalence estimates, being appropriate when there are few cases observed, provide measures on their uncertainty. The estimate is smoothed because, to estimate the rate of a municipality, information from the neighboring cities that make up the study region is used.

Another way is to consider this data in aggregate form by health macro-regions, although there is a loss of information in this process. According to the map presented in Figure 2, it is observed that the Serra region has a high prevalence (15.82) in relation to the general prevalence of RS (11.37) and that of the Midwest Region (4.95). Comparing with previous years, 2019 was an atypical year for the Valleys region, since in six consecutive years (2013-2018), the region had the highest prevalence. In 2019, only congenital heart disease and Down syndrome had lower prevalence, compared to the previous year.

The application of scan statistics for congenital heart disease, in the years 2011 to 2019, resulted in a cluster composed of the municipalities of Alvorada, Capivari do Sul, Glorinha, Gravataí, Porto Alegre and Santo Antônio da Patrulha (p-value <0.001, number of replications = 9999). The city of Porto Alegre has a high hospital infrastructure compared to other municipalities in the RS; in addition, reference hospitals in the capital provide medical care for several municipalities in the Metropolitan Region. Soon it is expected that, in addition to a large number of notifications due to the largest population of the city, these hospitals will collaborate in the identification and notification of several cases of CAs from the cities surrounding the capital. These facts may justify why the clusters generated by the Scan statistics in the analysis of different groups of CA are usually contained in the Metropolitan Region of Porto Alegre.

Figure 6 – Application tab "Scan Statistics". Result of scan statistics for congenital heart disease in the years 2010 to 2019[50]



Source: authors.

HOSTING ON RSTUDIO AND INSTALLATION VIA GITHUB

The application is available on a domain provided by shinyapps.io, a RStudio platform that offers free and paid plans for hosting Shiny applications, with access through any web browser by the link: **https://projetoanomaliascongenitas.shinyapps.io/ac_rs/**.

Using the tool on mobile devices and similar devices is discouraged, for the access via mobile can disfigure some images and make it difficult to choose filters and interactivity with some charts.

Access to the application via the web can be time-consuming, as the loading of the tool is subject to internet connection and server availability. One way to improve navigation is to run the application locally, for this it is necessary to have the R installed on the computer, along with packages described in Table 1 installed on the R. After that, you need to paste the following code into the **R** command line:

```
library(shiny)
runGitHub(repo = "App_Anomalias_Congenitas_RS", username =
"anomaliascongenitas",filetype = ".tar.gz")
```

All developed application code is in a public repository on GitHub (https://github.com/anomaliascongenitas/App_Anomalias_Congenitas_RS), under **Creative Commons license Attribution-NonCommercial 4.0 International (CC BY-NC 4.0)**, allowing any user to make suggestions or contributions.

FINAL CONSIDERATIONS

This work had as a proposal to present an application that makes it possible to assist the health surveillance of CAs in the state of RS, using the language **R** and the Shiny package, as well as showing examples of results generated by this tool. Among its functionalities, spatial visualizations of CAs cases between the years 2010 and 2019 are presented, through interactive maps, which allow to identify the spatial and spatio-temporal patterns of CA occurrences in the state. In addition, the calculations of the Moran Global Index, used to measure spatial autocorrelation, and the Scan statistic, to identify the clusters of CAs. The developed application allows to inform health managers and professionals about the geographical and temporal characteristics of the prevalence of CAs in the RS. Such information can be useful for better surveillance and monitoring of cases, in addition to collaborating in the planning of specific prevention actions for the state of RS.

The tool can be adapted and used as a reference for the spatio-temporal analysis, monitoring and implementation of CA surveillance strategies in others states of the Federation. In addition, it is expected to expand the model generated for RS from the development of other types of statistical analysis, such as, for example, the use of Bayesian hierarchical models in estimating the prevalence of CAs, which are appropriate techniques for mapping rare conditions. Another possibility includes the identification of possible risk factors related to the occurrence of CAs and the use of more specific information than those aggregated by municipality in the analysis of the data.

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TECHINICAL TEAM

PART I – REVIEWING PRIORITY CONGENITAL ANOMALIES

1 Congenital anomalies and the importance of notification

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2 Neural tube defects

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3 Congenital microcephaly

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4 Congenital heart diseases

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5 Oral clefts

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6 Genital abnormalities and disorders in sexual differentiation

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7 Congenital anomalies of the limbs

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8 Abdominal wall defects

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9 Down syndrome

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10 Prevention of congenital anomalies

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PART II – EXPERIENCE REPORTS AND TOOLS FOR EPIDEMIOLOGICAL SURVEILLANCE

11 From the public health emergency due to the increase in the occurrence of microcephaly to the surveillance of congenital anomalies: the experience of the Brazilian Ministry of Health

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12 From the public health emergency of microcephaly to the surveillance of congenital anomalies: the Pernambuco experience

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13 Congenital anomalies in the Live Birth Information System, 2001-2020: report of experience of the management of the system in the city of São Paulo

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14 The global birth defects web application (app) for the description and coding of congenital anomalies

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15 Web Application (app) of free access for monitoring congenital anomalies: the case of Rio Grande do Sul

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