Published in final edited form as:

Am J Med Genet C Semin Med Genet. 2011 November 15; 0(4): 358–373. doi:10.1002/ajmg.c.30324.

Sirenomelia: An Epidemiologic Study in a Large Dataset From the International Clearinghouse of Birth Defects Surveillance and Research, and Literature Review

IÊDA M. ORIOLI[1,2,*], **EMMANUELLE AMAR**[3], **JAZMIN ARTEAGA-VAZQUEZ**[4], **MARIAN K. BAKKER**[5], **SEBASTIANO BIANCA**[6], **LORENZO D. BOTTO**[7,8], **MAURIZIO CLEMENTI**[9], **ADOLFO CORREA**[10], **MELINDA CSAKY-SZUNYOGH**[11], **EMANUELE LEONCINI**[12], **ZHU LI**[13], **JORGE S. LÓPEZ-CAMELO**[2,14], **R. BRIAN LOWRY**[15], **LISA MARENGO**[16], **MARÍA-LUISA MARTÍNEZ-FRÍAS**[17,18,19], **PIERPAOLO MASTROIACOVO**[12], **MARGERY MORGAN**[20], **ANNA PIERINI**[21], **ANNUKKA RITVANEN**[22], **GIOACCHINO SCARANO**[23], **ELENA SZABOVA**[24], and **EDUARDO E. CASTILLA**[2,14,25]

[1]ECLAMC (Estudo Colaborativo Latino Americano de Malformações Congênitas) at Departamento de Genética, Instituto de Biologia, Rio de Janeiro, Brazil [2]INAGEMP (Instituto Nacional de Genética Médica Populacional), Rio de Janeiro, Brazil [3]Rhone-Alps Registry of Birth Defects REMERA, Lyon, France [4]Departamento de Genética, RYVEMCE (Registro y Vigilancia Epidemiológica de Malformaciones Congénitas), Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, México City, Mexico [5]Eurocat Northern Netherlands, Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands [6]Dipartimento Materno Infantile, Centro di Consulenza Genetica e di Teratologia della Riproduzione, Laboratorio di Citogenetica, P.O. Garibaldi, Nesima, Catania, Italy [7]Division of Medical Genetics, Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, Utah [8]Utah Birth Defect Network, Utah Department of Health, Salt Lake City, Utah [9]Department of Pediatrics, University of Padua, Clinical Genetics Unit, Padua, Italy [10]Metropolitan Atlanta Congenital Defects Program, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia [11]Department of Hungarian Congenital Abnormality Registry and Surveillance, National Center for Healthcare Audit and Inspection, Budapest, Hungary [12]Centre of the International Clearinghouse for Birth Defects Surveillance and Research, Rome, Italy [13]National Center for Maternal and Infant Health, Peking University Health Science Center, Beijing, People’s Republic of China [14]ECLAMC at CEMIC (Centro de Educación Médica e Investigación Clínica), Buenos Aires, Argentina [15]Alberta Congenital Anomalies Surveillance System, Alberta Health & Wellness, Calgary, Alberta, Canada [16]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Texas [17]ECEMC (Spanish Collaborative Study of Congenital Malformations), Centro de Investigación sobre Anomalías Congénitas (CIAC), Instituto de Salud Carlos III (ISCIII), Madrid, Spain [18]CIBER de Enfermedades Raras (CIBERER) (Centre for Biomedical Research on Rare Diseases),

[*]Correspondence to: Iêda M. Orioli, Departamento de Genética, Universidade Federal do Rio de Janeiro, Caixa Postal 68.011, 21944-970 Rio de Janeiro, Brazil. orioli@centroin.com.br.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Madrid, Spain [19]Department of Pharmacology, Faculty of Medicine, Universidad Complutense de Madrid, Spain [20]CARIS, the Congenital Anomaly and Register for Wales, Singleton Hospital, Swansea, United Kingdom [21]Tuscany Registry of Congenital Defects (RTDC), Epidemiology Unit, IFC-CNR, Pisa, Italy [22]The Finnish Register of Congenital Malformations, National Institute for Health and Welfare, THL, Helsinki, Finland [23]Birth Defects Campania Registry, Medical Genetics Dept, General Hospital "G. Rummo" Benevento, Italy [24]Slovak Teratologic Information Centre, Slovak Medical University, Bratislava, Slovak Republic [25]ECLAMC at Laboratório de Epidemiologia de Malformações Congênitas, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Abstract

Sirenomelia is a very rare limb anomaly in which the normally paired lower limbs are replaced by a single midline limb. This study describes the prevalence, associated malformations, and maternal characteristics among cases with sirenomelia. Data originated from 19 birth defect surveillance system members of the International Clearinghouse for Birth Defects Surveillance and Research, and were reported according to a single pre-established protocol. Cases were clinically evaluated locally and reviewed centrally. A total of 249 cases with sirenomelia were identified among 25,290,172 births, for a prevalence of 0.98 per 100,000, with higher prevalence in the Mexican registry. An increase of sirenomelia prevalence with maternal age less than 20 years was statistically significant. The proportion of twinning was 9%, higher than the 1% expected. Sex was ambiguous in 47% of cases, and no different from expectation in the rest. The proportion of cases born alive, premature, and weighting less than 2,500 g were 47%, 71.2%, and 88.2%, respectively. Half of the cases with sirenomelia also presented with genital, large bowel, and urinary defects. About 10–15% of the cases had lower spinal column defects, single or anomalous umbilical artery, upper limb, cardiac, and central nervous system defects. There was a greater than expected association of sirenomelia with other very rare defects such as bladder exstrophy, cyclopia/holoprosencephaly, and acardia-acephalus. The application of the new biological network analysis approach, including molecular results, to these associated very rare diseases is suggested for future studies.

Keywords

sirenomelia; caudal regression spectrum; twinning; maternal age; world prevalence; caudal dysgenesis

INTRODUCTION

According to Stevenson [2006] "Sirenomelia is a limb anomaly in which the normally paired lower limbs are replaced by a single midline limb." This is probably the best definition in the literature because it does not use the term "fusion." Other definitions characterize sirenomelia as different degrees of fusion between the lower limbs. However, the term "fusion," derived from Latin *fundere*, should be avoided because, as a noun derived

from Latin *fundere*, it implies the uniting of separated parts, in this case the para-medial limb buds, which is an unproven mechanism of production for sirenomelia.

Definition and Diagnostic Challenges

Even when sirenomelia seems to be a discrete and well-defined anomaly, some difficulties can be encountered in its delineation. On one hand, if its definition as the presence of an axial positioned single lower limb is accepted, the first three of the seven types in Stocker and Heifetz [1987] classification (see next section on Classification) cannot be included as sirenomelias since they do not present an axial single lower limb. On the other hand, extended crural or multiple crural-popliteal-talus pterygia can overlap with Type-I sirenomelia from the clinical and radiological standpoints. Furthermore, when associated with other unrelated anomalies such as craniofacial, sirenomelia may overlap with multiple pterygium syndromes of the Bartsocas–Papas [Bartsocas and Papas, 1972], or Aslan type [Aslan et al., 2000], OMIM 263650 and 605203, respectively. However, popliteal pterygia associated with caudal regression spectrum (CRS; caudal dysgenesis) were described in a child born from a diabetic mother [Al Kaissi et al., 2008].

ICD-10 lacks a specific code for sirenomelia, which must be coded as Q87.2 “congenital malformation syndromes predominantly affecting limbs.” This is a serious limitation for the study of time-space clusters, as reported from South America [Castilla et al., 2008; Orioli et al., 2009], as well as for statutory birth defects registries that only use ICD-10 as the basis for their coding system for congenital anomalies. The pediatric extension of ICD10 (BPA) has a specific code for “sirenomelia syndrome” which is Q87.24.

Prenatal diagnosis of sirenomelia by ultrasound is impaired by the coexisting oligohydramnion resulting from the frequently associated bilateral renal a/dysgenesis [Wasnik and Lalchandani, 2010]. However, there is a narrow window, between weeks 8 and 16 of gestation, that is, when the limb structures are visible to ultrasound, and the amniotic fluid still depends mainly from maternal production, when visualization of sirenomelia is possible [Valenzano et al., 1999; Schiesser et al., 2003]. Nevertheless, first trimester ultrasono-graphic examinations are infrequent and only a few cases of early diagnosed sirenomelia have been reported [Blaicher et al., 2001; Carbillon et al., 2001; Akbayir et al., 2008]. Patel and Suchet [2004] applied color and power Doppler ultrasound to diagnose second and third trimester fetuses with sirenomelia mainly based on fetal vascular images.

Classification

Sirenomelia was first classified into three types according to the number of feet and named sympus apus, monopus, and dipus, for none, one, or two feet, respectively [Foerster, 1861–1865]. A more adequate classification of sirenomelia is that of Stocker and Heifetz [1987] in which seven types are defined: I, all thigh and leg bones present; II, single fibula; III, absent fibulae; IV, partially fused femurs, fused fibulae; V, partially fused femurs, absent fibulae; VI, single femur, single tibia; VII, single femur, absent tibiae. However, none of these classifications follow a dysmorphogenetic rationale, proposing nothing more than discrete groupings of a continuous spectrum.

Historical Aspects

Very rare congenital defects (VRDs), having an expected occurrence rate of 1 per 100,000 or lower, were expected to happen only once every several generations in most ancient populations at the time of polytheist religions, when several VRDs became mythological figures. Early human populations were mostly rural, and urban areas seldom passed over 1,000 inhabitants, except for classical Athens, one of the first known city-state, with about 100,000 residents in the late 5th and 4th century BC [Scheidel, 2008]. Thus, even with a natality rate as high as 50 per thousand per year, no more than one case of a given VRD every 20 years or more was to be expected (i.e., approximately one case per generation, assuming 25 years per generation). Pictured or written descriptions probably facilitated the recording and/or historical recognition of a given VRD. Nevertheless, the large time-lapse between occurrences in ancient populations probably allowed for magical or mythological thinking about such defects [Stahl and Tourame, 2010].

Sirenomelia, cyclopia, and, to a lesser degree, conjoined twins received special attention in most fantasies, mythologies, and religions, in which these defects seem to have been taken more as caprice of nature than as real monstrosities. Sirenomelia is referred as “mermaid” in mythology, that is: as a female, more frequently than as the male counterpart “merman,” or Triton type sirenomelia, probably due to the more attractive and esthetic sensual attributes, as bosom, eyes, and hair in the female gender when external genitalia was omitted.

Embryology

Normal development: Morphology—In the mouse, each lower limb derives from a different para-medial developmental field determined at gastrulation due to the expression of *Pitx1*-dependent *Tbx4* [Ouimette et al., 2010]. This process occurs over 25 days, beginning at week 4 after fertilization, and by the end of the eighth week, the limb is perfectly formed. Lower limbs are delayed 2 days in comparison to forelimbs. The trigger for limb bud initiation is unknown, even though fibroblast growth factors 8 and 10 are hypothesized as being involved [Agarwal et al., 2003].

Limb development is a continuous process that encompasses meso- and ectodermal components and is divided into four stages: the bud (outgrowth), the paddle (dorso-ventral flattening), the plate (relative expansion of the distal end), and the rotation (around the proximo-distal axis). In the latter stage, the position of the limb buds relative to the trunk change due to the differentiate growth of the cartilage model that continues to elongate the limb, with different parts growing at different rates. Lower limbs twist around their proximo-distal axis medially (internally) bringing the great toe to the midline from its initial postaxial position [Larsen, 1993].

Abnormal development: Dysmorphology—Two main non-mutually exclusive hypotheses were advanced to explain the abnormal development of the lower limbs leading to sirenomelia: blastogenetic and vascular. The former hypothesis postulates a primary anomaly in the development of the caudal axial mesoderm [Källén and Winberg, 1974; Opitz et al., 2002; Kjaer et al., 2003; Garrido-Allepuz et al., 2011], while the latter is based on an abnormal development of the umbilical vessels resulting in a deficient blood supply of

the caudal part of the embryo [Kampmeier, 1927; Hentschel et al., 2006]. This latter hypothesis is supported by observations of caudal "vascular steal" through a persistent vitelline artery [Stevenson et al., 1986; Bianchi et al., 2000; Patel and Suchet, 2004]. There have been several case reports supporting the vascular hypothesis [Hentschel et al., 2006; Duesterhoeft et al., 2007] as well as some rejecting it [Jaiyesimi et al., 1998]. Since these hypotheses are extended to the whole CRS, as well as to other associated defects, it is feasible that both hypotheses are valid, even allowing for additional possible pathogenetic mechanisms to be proposed in the future.

Sirenomelia and caudal regression spectrum (CRS)—The concept of sirenomelia as the most severe extreme of CRS was advanced by Duhamel [1961], fitting within the general concept of very rare defects being extremes of dysmorphologic spectra [Castilla and Mastroiacovo, 2011]. While sirenomelia and CRS without sirenomelic share some common characteristics as male sex preference, maternal diabetes, and absent sacrum [Duesterhoeft et al., 2007], associated defects as single umbilical artery, lethal renal a/dysgenesis, and oligohydramnios-related deformities are much more frequent in the former than in the latter [Källén and Winberg, 1974; Martínez-Frías et al., 2008]. Thus, the concept of sirenomelia and caudal dysgenesis being at the severest end of the same CRS, proposed by Thottungal et al. [2010] makes sense and incorporates most observations made until now [Goodlow et al., 1988; Guidera et al., 1991; Das et al., 2002].

Genetics and Clinical Genetics

As is the case with most, if not all congenital anomalies, sirenomelia is etiologically heterogeneous. No instances of familial recurrence of sirenomelia have been reported. However, under the pathogenetic concept of sirenomelia as part of the CRS, familial cases are known. A pair of sirenomelic concordant identical twins was reported by Di Lorenzo et al. [1991]. Four siblings with renal defects, one of them with sirenomelia [Selig et al., 1993], are considered to have renal adysplasia (OMIM 191830), The renal adysplasia patients can have mutations in the *RET* gene (OMIM 164761) located at 10q11.2 or in the uroplakin IIIA gene (*UPK3A*; OMIM 611559) located at 22q13.31. Sirenomelia was reported in one case with an extra small bisatellited marker chromosome identified as the proximal part of the long arm of chromosome 22 [Jensen and Hansen, 1981]; probably this case was an earlier example of *UPK3A* gene deletion.

Molecular studies in CRS show a variety of specific anomalies: mutations in the *VANGL1* gene mapped at 1p13 for CRS [Kibar et al., 2007], a homeo-box gene on chromosome 7q36 for anorectal atresia [Lowry et al., 2007], and mutations in *HLXB9* gene for the Currarino syndrome reported by Köchling et al. [2001]. No gene mutations have been reported in sirenomelia patients. No *SHH* mutations were found by Vargas et al. [1998] in sacral agenesis/sirenomelia cases. Sirenomelia can occur in crosses between specific mice strains and as consequence of mutations that increase retinoic acid, as observed in gene-knockouts of *Cyp26* that codifies for a retinoic acid degrading enzyme (CYP26), recently revised by Pennimpede et al. [2010].

Zakin et al. [2005] have shown that the lack of bone morphogenetic protein 7 (*Bmp 7*) in combination with half a dose or complete loss of twisted gastrulation (*Tsg*) protein cause sirenomelia in mice. Tsg is one of several regulators of Bmp, whose gradient determines the dorso-vertebral patterning in vertebrate and invertebrate embryos. The same team has earlier described that in the absence of *Tsg*, the loss of one copy of *Bmp4* results in holoprosencephaly and branchial arc defects [Zakin and De Robertis, 2004]. Then, *Tsg* and *Bmp* interaction seems doubly interesting to the VRD studies, considering the occurrence of both conditions, sirenomelia and holoprosencephaly, in the same human newborn [Martínez-Frías et al., 1998b].

A so-called “mermaid (merm) mutant” (*Nup133*^{merm} mutation) was described disrupting mouse (*mus musculus*) gastrulation which is a functional null allele of nucleoporin Nup133, a constituent of the conserved Nup107-160 complex [García-García et al., 2005]. The phenotype in mice includes exencephaly, shortened trunk, irregularly segmented somites, and a minimal tail bud.

Epidemiology: Prevalence, Risk Factors

Prevalence—The birth prevalence of sirenomelia varies from 1 to 2 per 100,000, depending on the denominator definition and case ascertainment since one-third of the cases of sirenomelia are stillborn [Källén et al., 1992; Castilla and Orioli, 2004]. From 10% to 15% of occurrences are in twin births, mostly monozygous [Valenzano et al., 1999].

Due to the absence of external genitalia and infrequent information on gonadal or chromosomal sex, data on sex distribution are very scarce. Nonetheless, the limited information available indicates male sex preference [Duesterhoeft et al., 2007], or does not indicate any substantial sex preference [Källén et al., 1992].

Clusters—A time-space cluster of sirenomelia in 2005 in the city of Cali (Colombia) was reported by ECLAMC (Spanish acronym for the Latin American Collaborative Study of Congenital Malformations) [Castilla et al., 2008; Orioli et al., 2009]. As with most reported epidemics of congenital anomalies, except for phocomelia due to maternal thalidomide exposure this cluster ended spontaneously, without identification of its cause. The most interesting aspect of this cluster is the nearly simultaneous rise and fall in the birth prevalence rates of sirenomelia and cyclopia, supporting the concept of shared causal factors.

Maternal age—An international study showed an U-shaped curve with increased risk for sirenomelia at young and old maternal ages: under 20, and over 40 years old [Källén et al., 1992]. However this observation has not been investigated further.

Maternal diabetes—One-fifth of published sirenomelia cases were delivered to diabetic mothers, the offspring of whom are reported to have a prevalence of one in 200 births for a sirenomelia/caudal regression (CRS) infant [Gurakan et al., 1996; Martínez-Frías et al., 1998a; Al-Haggar et al., 2010]. However, in a 15-year pathology series Bruce et al. [2009] found a history of maternal diabetes in three out of nine CRS cases, but in none of six cases of sirenomelia.

Some associations with sirenomelia and/or CRS such as VATER association [Castori et al., 2010], pterygia [Al Kaissi et al., 2008], and twinning [Zaw and Stone, 2002] present with a history of maternal diabetes providing clues for a common risk factor. Castori et al. [2010] report a diabetic mother having had infants with sirenomelia and VATER association from two out of her three pregnancies, indicating a possible causal relationship between maternal diabetes and these two early blastogenic defects. Beside this observation, these authors also speculate on the pathogenetic identity of both anomalies belonging to the same dysmorphogenic spectrum. These conclusions were based not only on the reported case but also on two previously published observations [Valenzano et al., 1999; Castori et al., 2008].

Environmental risk factors—Several chemicals have been reported to induce sirenomelia/CRS in experimental mammals, including retinoic acid in mice [Padmanabhan, 1998], cadmium and lead in golden hamsters [Hilbelink and Kaplan, 1986], and ochratoxin A in chick embryos [Wei and Sulik, 1996]. Human reports on prenatal exposures include cocaine [Sarpong and Headings, 1992], and an undefined “snuff” [Taghavi et al., 2009]. A thorough review by Holmes [2002] found no plausible teratogens associated with sirenomelia.

Associated and Combined Anomalies

Since sirenomelia is not well delineated, relative to the CRS, it is difficult to specify which congenital anomalies are pathogenetically associated with sirenomelia. Association of sirenomelia/CRS with component anomalies of the Potter sequence is obviously expected due to the an/oligohydramnios produced by the usually associated severe and lethal renal a/dysgenesis [Savader et al., 1989; Al-Haggar et al., 2010]. An association between sirenomelia/CRS and VATER association could be explained by both deriving from an early blastogenic insult, when the potential embryo exists in a single developmental field [Opitz et al., 2002]. Epidemiological data supporting this were provided by Duncan and Shapiro [1993], Duncan et al. [1991], and Schüler and Salzano [1994]. Further support came from clinical observations, in which maternal diabetes provided an etiological ground for both anomalies [Kalter, 1993; Valenzano et al., 1999; Castori et al., 2010], as well as from more recent experimental studies with adriamycin in rats and mice [Abu-Hijleh et al., 2000; Dawrant et al., 2007]. The alternative approach of searching for sirenomelia/CRS in association with VATER in the same patient also provided support to this preferential association [Botto et al., 1997; Rittler et al., 1996].

Another potential similarity of sirenomelia/CRS with VATER association is imperforate anus, the A in VATER acronym, which Duhamel [1961] proposed as the mildest end of the CRS. However, during the survey of the epidemic of sirenomelia in the city of Cali, variations in the birth prevalence of imperforate anus was analyzed as a sentinel phenotype for minor forms of CRS, and no concomitant rise in frequency was detected [Castilla et al., 2008].

The reported association of sirenomelia/CRS with neural tube defects (NTD), mainly with spina bifida, is to be expected since the lower spine is affected in this anomaly [Källén et al., 1992]. A more extended NTD in a fetus with sirenomelia and acardia was reported by

Halder et al. [2001]. Sirenomelia and popliteal or multiple pterygia were reported in some cases [Aslan et al., 2000], and a common causality due to maternal diabetes was proposed [Al Kaissi et al., 2008].

Combined VRD—We are here naming as "combined" VRD the concurrence of two or more of the eight defects (acardia, amelia, phocomelia, conjoined twins, cyclopia, sirenomelia, bladder, and cloaca esxtrophies) reported in this series of articles with material from ICBDSR [2009]. This is to distinguish them from the commonly named "associated" for the coexistence of sirenomelia with other unrelated congenital anomalies. The occasional coincidence of more than one VRD in the same individual is difficult to accept as chance occurrence, and a common etiopathogenic mechanism is more likely to explain it since most of them are presumably early blastogenic defects [Opitz et al., 2002].

Sirenomelia–Cyclopia—There is evidence for concurrence of sirenomelia and cyclopia in the same patient [Martínez-Frías et al., 1998b], being associated with similar epidemiological risk factors [Källén et al., 1992]; being observed in the same clusters [Castilla et al., 2008], and for potentially sharing a similar pathogenetic mechanisms [O'Railly and Müller, 1989].

Sirenomelia–Acardia—Concurrence in the same case was documented by Zanforlin Filho et al. [2007], as well as by Halder et al. [2001].

Sirenomelia/CRS and situs inversus in the same case were reported by Langer et al. [1999] and Rougemont et al. [2008].

Prognosis, Treatment, Survival, and Prevention

Except for very rare instances, sirenomelia is a lethal condition in the perinatal period, hampering any intent of treatment. In a large set of consecutive birth series (10.1 million births), 97 cases of sirenomelia were identified, 35 of them in stillbirths, and 62 in live births who died shortly after birth [Källén et al., 1992].

In sirenomelia, the prognosis for morbidity, survival, and quality of life depends almost exclusively on the presence or not of congenital anomalies affecting vital organs, such as renal a/dysgenesis [Messineo et al., 2006]. There is documentation of one individual with sirenomelia born in the early 1990s that was claimed to be the second surviving case of sirenomelia known [Murphy et al., 1992], additionally, there is documentation in 2003 of a 4-year-old patient reported to be the fifth surviving patient [Stanton et al., 2003].

Only about 1% of cases survive the first week of life. Among these, three cases with Stocker and Heifetz [1987] types I to III of sirenomelia were widely publicized through the lay press. One of them was born in August 1999 in Kennebunkport, Maine, USA, having a small remnant of a kidney, 15 cm of large intestine, one ovary, and absent uterus and external genitalia. She underwent two kidney transplants, dying at the age of 10 years from pneumonia. The other two cases still are still alive at present (in 2011), both of them, apparently having no other major anomalies, and who underwent successful surgery for leg

separation. However, as mentioned above, these milder types could not be true sirenomelias, but pterygia involving just the soft tissues of lower limbs.

There is room for the primary prevention of sirenomelia through the appropriate pre-conceptional diagnosis and treatment of all types of diabetes that can lead to an exposure of the early embryo to high levels of maternal glycemia. In theory, as many as 20% of all cases of sirenomelia could be avoided [Kadian et al., 2008; Delissaint and McKyer, 2011].

In order to expand on the limited epidemiologic information on sirenomelia, we conducted a descriptive analysis of prevalence data collected on sirenomelia by 19 program members of the International Clearinghouse for Birth Defects Surveillance and Research (hereafter referred to as “the Clearing-house”). In this analysis, we examined the variation in prevalence by program, over time, and by selected maternal and infant characteristics.

METHODS

The Clearinghouse collects data from 46 member birth defect surveillance programs around the world, sampling out data from 37 countries. Six countries have two or more participating programs, and one (ECLAMC: Estudo Colaborativo Latino Americano de Malformações Congênitas) including hospitals from 10 different South American countries. Each program submits data in the same format to the Clearinghouse for the annual report, which includes detailed descriptions of each member registry [ICBDSR, 2009].

Study Design and Cohorts

This was a retrospective cohort study from population-based and hospital-based birth defect surveillance programs. Nineteen programs from North and South America, Europe, China, and Australia provided data on sirenomelia, ascertained from a total birth population of almost 25.3 million births. Birth years included in the study ranged from 1968 to 2006, and varied by program. Births included live births, stillbirths, and, for some but not all programs, elective pregnancy terminations for fetal anomalies (ETOPFA).

Cases with sirenomelia were classified according to the number of defects unrelated to the CRS [Orioli et al., 2009]. Defects considered as related to sirenomelia include urinary, genital, large bowel, low spinal column, single umbilical artery, and oligohydramnion derived defects. Other types of defects were grouped into 17 sets: other spinal column or rib, small intestine, esophagus or diaphragmatic, cardiac, upper limb, abdominal or thoracic wall, ear, eye, oral cleft, other facial, holoprosencephaly, skin tag, situs inversus, hydrocephalus, CNS, other artery, and other defects; and each of them subdivided into different sub-sets under different ad hoc codes. The cases with sirenomelia were also separated into isolated cases (i.e., cases with no other defect outside the sirenomelia spectrum reported in the same case); and MCA (multiple congenital anomalies) cases (i.e., cases with associated non-sirenomelia-spectrum defects reported).

Programs were asked to provide de-identified case records following a common protocol, with information on phenotype, genetic testing, and selected demographic and prenatal information. Further details can be found in Castilla and Mastroiacovo [2011] in this issue.

Case Review

All records were reviewed by two experienced dysmorphologists (PM, IMO). When information was unclear or missing, clarification and further data were requested from the participating program. All cases were reported verbatim and centrally classified.

Inclusions and Exclusions

Included were cases of sirenomelia, as identified by the participating programs. Cases with extended crural pterygium, and non-medial single lower limb, suggestive of lower limb amelia were excluded. Spontaneous abortions (less 500 g, or 20 weeks gestation) were excluded among cases and denominators.

Statistical Methods

Occurrence was expressed as total prevalence (number of live births, stillbirths and ETOPFA with sirenomelia per 100,000 births) with its 95% confidence intervals (CI). For each program the expected number of cases was calculated under the hypothesis of a homogeneous prevalence among all programs. Using the expected values, we calculated the exact Poisson probabilities of observing N or more cases (P ($N \geq X$)) in each registry. Maternal age-specific prevalence ratios were calculated using the number of total cases and all births (live births and stillbirths) data by 5 years maternal age groups and using the 25–29 years group as the reference group. Pearson correlation was used as a measure of correlation between the prevalence of sirenomelia and two variables: the number of births and the proportion of ETOPFA in each registry. The 95% CI were computed using the Poisson distribution. Statistical test significance was set to $P < 0.05$. Statistical analyses were done with Stata software, version 10.0 [StataCorp, 2007].

RESULTS

Prevalence

The total number of births and of sirenomelia cases is given in Table I for each of the 19 surveillance programs members of the International Clearing-house for Birth Defects Surveillance and Research (ICBDSR). A total of 249 cases with sirenomelia were identified among 25,290,172 births, for a birth prevalence of 1 per 100,758 births or 0.98 per 100,000 (95% CI 0.87–1.11). The proportion of ETOPFA was 24.5% considering all reported cases. ETOPFA was not permitted in two surveillance programs (Mexico RYVEMCE: Registro y Vigilancia Epidemiológica de Malformaciones Congénitas; and South America ECLAMC), and was not recorded in another two (Spain ECEMC: Spanish Collaborative Study of Congenital Malformations; and China, Beijing). Excluding these four programs the proportion of ETOPFA was 49.5%. There was no correlation between the proportion of cases of sirenomelia submitted to ETOPFA and the sirenomelia prevalence ($r = 0.25$; $P = 0.37$).

Figure 1 shows the sirenomelia prevalence with their 95% CI in the different surveillance programs. Hungary (0.33 per 100,000; 95% CI 0.16–0.61; $P < 0.0001$) as well as Italy Campania (0.16 per 100,000; 95% CI 0.00–0.87; $P < 0.013$) show statistically significant lower prevalence, suggesting under-ascertainment. Five programs show a statistically

significant higher sirenomelia prevalence: Mexico RYVEMCE: 2.36 (95% CI 1.53–3.49; *P* <0.0001), South America ECLAMC: 1.36 (95% CI 1.04–1.74; *P* <0.006), Italy North-East 1.69 (95% CI 1.03–2.60; *P* <0.009), Canada Alberta (1.6 per 100,000; 95% CI 0.93–2.56; *P* < 0.021), and Wales (2.25 per 100,000; 95% CI 0.73–5.25; *P* <0.024). If we discard the two registries with under-ascertainment only the Mexican registry had a higher prevalence than the other registries.

There was no correlation between the sirenomelia prevalence and number of births in each surveillance program (r =0.03; *P* =0.92). More than half (53.4%) of the sirenomelia cases in this study were provided by four reporting surveillance programs: South America ECLAMC, France Central East, Mexico RYVEMCE, and Italy North East.

Secular Variation

There is variation in the annual frequencies of sirenomelia within each of the 19 programs. However, there were no evident secular trends.

Maternal Age

For the maternal age analyses we excluded sirenomelia cases and births from China (before 1997 and after 2003), Italy North-East, and Italy Sicily because the number of births by maternal age was not available. Maternal age was analyzed in six groups: less than 20 years, 20–24, 25–29, 30–34, 35–39, and 40 years or older. In Table II the sirenomelia prevalence for each maternal age group and the prevalence ratios for maternal age groups relative to the reference age group of 25–29 years with corresponding 95% CI are shown. There was a clear gradient (Fig. 2) in the sirenomelia prevalence from younger to older maternal age groups (*P* <0.01), with the prevalence ratio for maternal age less than 20 years increased significantly (1.71; 95% CI 1.13–2.59). When the cases were separated into isolated or MCA (multiple congenital anomalies) groups (Table III), the same prevalence trend and significant prevalence ratio remained only for the MCA group.

Sex

The sirenomelia spectrum of defects includes external and internal genital defects; thus making sex determination difficult. Autopsy findings were more helpful in the sex determination since only 12 patients (8 females and 4 males) had a karyotype result. In 11% of cases the sex was unknown and 47.0% were described as having ambiguous genitalia. The proportion of males (49%) did not differ from the 51% expected in the sample of 105 patients with determined sex. When grouping patients into isolated and associated defects, the proportion of unspecified sex was smaller in the MCA (7.1%) than in the isolated group (14.6%). The ETOPFA cases had 47% of males among the small sample of 43 patients with determined sex; information on sex was missing in only 3%, and not determined in 18%.

Other Risk Factors

Information on risk factors (i.e., mainly maternal exposures during pregnancy) was not available for most of the registries. Among 133 informative cases, there were seven (5%) with maternal diabetes. Misoprostol first trimester exposure was found in one case, and fever in six cases (4.5%).

None of the 249 sirenomelia cases had any indication of other family members being affected by this or CRS.

Descriptive Analysis of Sirenomelia Patients

There were 123 isolated cases (49%), and 126 (51%) with other non-related defects. In Table IV we present the comparison of sex, outcome, birth weight, gestational age, parity, previous spontaneous abortion, plurality, maternal age, parental age difference, and maternal education between isolated and MCA sirenomelia cases. The associations with maternal age and sex were already described above. Pregnancy outcomes among sirenomelia cases were: liveborn 47%, stillbirths 28.5%, and ETOPFA 24.5%. The proportion of ETOPFA was slightly higher in MCA cases (28.6%) than in the isolated cases (20.3%), but the difference did not reach statistical significance (P =0.13). For other pregnancy outcomes, the isolated and MCA cases had similar distributions.

Only 11.1% of the sirenomelia births weighed more than 2,500 g. The proportion of cases who were low birth weight did not differ between isolated and MCA cases. Prematurity was found in 71.2% of the cases, with 25.6% below 32 weeks, and 37.6% between 33 and 36 weeks of gestation, and no difference between isolated and MCA cases. The proportions of first births, previous spontaneous abortion, years of parental age difference and of maternal education did not differ between the isolated and MCA groups of sirenomelia cases, and were similar to those expected in the general population. However, the proportion of multiple births among sirenomelia cases was 8% versus an expected rate of 1% or slightly more in the general population.

Related and Unrelated Defects in Sirenomelia

Single midline lower limb, reno-urinary, genital, large bowel, low spinal column, single or anomalous umbilical artery, and oligohydramnios-derived defects were in this work considered as part of the sirenomelia sequence. Cases with sirenomelia that had other different defects were classified as MCA cases. Cases with inadequately described or minor defects were not considered. The isolated group (I) comprised of 123 infants (49%), and the remaining 126 (51%) were divided in groups having 1 (28%), 2 (16%), and 3 or more unrelated defects (7%), The unrelated defects formed 17 groups of defects coded ad hoc as explained in the Methods Section. Since the description of the specific defects is higher in MCA groups with 812 specific defects described in 126 patients (6.44 defects by patient) than in the isolated group with 346 specific defects in 123 patients (2.81 defects by patient), we show the frequency of related defects only in MCA group or in the total sample.

Related Reno-Urinary Defects

Urinary defects were mentioned in 57.1% of MCA cases and in 46.6% of all cases. Total absence of the reno-urinary tree was described in 73.3% of informative cases. Unilateral kidney agenesis or bilateral hypoplasia was seen in 9.5%, cystic or dysplastic kidneys in 12.9%, horseshoe kidney (including horseshoe cystic kidney) in 5.2%, and hydronephrosis in 4.3% of the cases.

Related Genital Defects

Genital defects were described in 59.5% of MCA and in 57% of all patients. Absence of total genitalia absence was reported in 59.9%, and ambiguous genitalia in 25.4% of all 142 informative patients.

Related Lower Spinal Column Defects

Most of the sirenomelia cases (80.2% in MCA groups) had no lower spinal column defects described, with this defect being present in 16% of all cases. Sacral or sacrococcygeal absence was present in 59.9% of the 40 informative cases, and the sacral or sacrococcygeal defects described in 25.4% of these cases.

Related Large Bowel Defects

Defects of the large intestine were described in 62.7% of MCA cases, being present in 53.4% of all cases. Anal atresia was the most frequent defect, present in 91.0% of 133 informative cases. Anal and intestinal duplication were described in three cases.

Other Related Defects

Single or anomalous umbilical artery was present in 16.5% and oligohydramnion related defects in 24.9% of all cases. Among the 62 cases with these defects, 12.4% were described as Potter anomalies and 7.2% as lung hypoplasia.

Unrelated Defects

The 17 groups of unrelated defects observed in the 126 MCA sirenomelia patients were defined in the Methods Section. Below they are summarized in the limb, trunk, and head regions.

Limbs

The commonest non-related defects (30.2%) among the MCA group were those in the upper limb group. These latter defects included: 14.3% of radial aplasia/hypoplasia, 7.9% described as upper limb reduction, and 3.2% as polydactyly or pre-axial polydactyly; lobster claw hands were described in three (2.4%) sirenomelia cases; postaxial limb reduction, webbed upper limbs and upper limb joint contractures, with one case each.

Trunk

Other or unspecified defects of spinal column and of ribs were described in 21.4% of MCA cases of sirenomelia. Cardiac defects were present in 20.6% of MCA cases, with 4.8% presenting as tetralogy of Fallot, 3.2% as single ventricle, and 2.4% as left heart hypoplasia. Defects of central nervous system were described in 19.0% of MCA cases, with spina bifida (mainly lower spina bifida) reported in 10.3%, and microcephaly in 2.4% of the cases. Esophageal atresia/fistula was described in 12.7% of MCA cases, defects of the diaphragm in 3.2% of such cases. In decreasing prevalence order, the following defects were also described: omphaloceles (5.6%) and other abdominal wall defects (4.0%). Other cases were reported as having abdominal wall defect and ectopia cordis, bladder exstrophy, bladder

exstrophy with cephalic celosomia, and gastroschisis (one case for each of these associations).

Head

Hydrocephalus was present in 8.7% of MCA cases. Microtia was described in 6.3% of MCA cases, and oral clefts in 5.1% of MCA cases. Eye defects were reported in 5.6% of MCA cases, with 4.0% being microphthalmia. Several cases (11.9%) had other facial defects, including ocular hypertelorism seen in 3.2% of the MCA cases.

Other

Arterial defects different from single or anomalous umbilical artery were described in 9.5% of MCA cases, with 4.0% being persistent superior vena cava. Duodenal atresia (4.8%), skin tag (2.4%), and holoprosencephaly (one case), were also described among the unrelated defects. Since hydrocephalus was frequent and could sometimes be considered as a heterotaxic defect, it is important to note that 5.6% of MCA patients presented with other heterotaxic defects such as dextrocardia, spleen agenesis or defect, and lung lobation anomalies.

Syndromes or Associations

Chromosomal syndromes are not common among the sirenomelia cases. Only 12 cases of sirenomelia had karyotype results and all such results were normal. Monogenic syndromes were not described in any cases. Considering the association with other VRD there were three cases combining sirenomelia and bladder exstrophy, one from Mexico registry and two, a twin pair, from South America. Acardia-acephalus were described in two cases with sirenomelia, one from Spain [Martínez-Frías, 2009] and one from South America. This last case presented also with cyclopia and was a case with acardia-acephalus, cyclopia, and sirenomelia. Also from South America there were one case with sirenomelia and conjoined twin and other probable case of sirenomelia–cyclopia, described as sirenomelia, medial cleft lip, and ocular hypotelorism. Another case from France presented with sirenomelia and holoprosencephaly.

DISCUSSION

Prevalence

The sirenomelia prevalence observed in this population of more than 25 million births of 0.98 per 100,000 births did not differ from previous estimates [Källén et al., 1992; Castilla and Orioli, 2004]. The lower prevalence observed in the Hungary registry could reflect some under-ascertainment since only 10% of the identified sirenomelias came from ETOPFA, a proportion lower than the percentage estimated from the 15 surveillance programs registering ETOPFA (49.5%). We observed statistically significant higher sirenomelia prevalence in the Mexican, South American, Italy North-East, and Canada Alberta registries, and also a lower than expected prevalence in the Italy Campania registry. However, if we exclude the data from Hungary and Italy Campania, only the Mexican registry had a higher sirenomelia prevalence than the other registries.

The higher prevalence observed in the Mexican registry has no direct explanation. Other registries with limited or no recording of ETOPFA (e.g., South America, Spain, and China) did not have a high prevalence of sirenomelia, so lack of ETOPFA does not seem to be a likely explanation. The Mexican population could be ethnically different from the other studied populations, having a higher proportion of Amerindians [Collins-Schramm et al., 2004]; however, it is unclear whether this characteristic is likely to account for the higher prevalence of sirenomelia. Only specific case–control studies can test this suggestion of an association of sirenomelia with ethnicity. A more specific hypothesis is that pre-gestational diabetes (e.g., diagnosed and undiagnosed type 2 diabetes), which may be more prevalent in the population covered by the Mexican registry than the populations of other registries since the prevalence of pre-gestational diabetes is reported to be higher among pregnant Hispanic women than among pregnant non-Hispanic white women [Lawrence et al., 2008]. However, we did not have adequate data on pre-gestational diabetes in our data to examine the possible association of maternal pre-gestational diabetes and sirenomelia.

There is a reasonable level of confidence in the certainty of the sirenomelia diagnosis in the 249 studied cases. However, unilateral lower limb amelia can sometimes be confounded with sirenomelia when the only lower limb has a median position. Since 40 cases (16%) were described only by the word sirenomelia, it is possible that diagnostic misclassification occurred in a few instances.

Maternal Age

The higher prevalence of sirenomelia observed in the younger maternal age group (less than 20) is a new finding in the epidemiology of sirenomelia. Since twinning and maternal diabetes are usually associated with sirenomelia, and both conditions are more likely to occur with older maternal age, the higher prevalence of sirenomelia we found in younger mothers was unexpected. Källén et al. [1992] suggested an increased risk of sirenomelia in offspring of young and older mothers, but such findings were not statistically significant. The higher sirenomelia prevalence we observed in younger mothers was evident in the MCA case group but not in the isolated case group. Since there was a similar prevalence gradient in the total data set, this lack of significance for the isolated case group could reflect low power of small sample sizes or, alternatively, indicate some etiologic difference between the isolated and the MCA case groups (e.g., difference in pre-gestational diabetes).

Sex

The sex in sirenomelia was generally based on gonadal or, rarely, on chromosomal examination, which explains why almost half of the cases had undetermined sex. However, the cases with determined sex did not show a higher prevalence of males as suggested previously [Duesterhoeft et al., 2007]. In a small sample of sirenomelia cases (n =32) studied by Källén et al. [1992], there were more females than males. However, this difference was not statistically different from the expected male-to-female sex ratio.

Other Risk Factors

Due to a lack of systematically collected data on maternal conditions, we were unable to confirm previous reports that one-fifth of mothers of sirenomelic infants have diabetes

[Gurakan et al., 1996; Martínez-Frías et al., 1998a; Al-Haggar et al., 2010]. Our results, however, were more consistent with those of other authors [Stocker and Heifetz, 1987; Duncan and Shapiro, 1993; Lynch and Wright, 1997; Duesterhoeft et al., 2007] that reported a lower prevalence of maternal diabetes (i.e., less than 4%) among cases of sirenomelia. The 5% of diabetic mothers in our sample of 133 informative cases coincide with the suggestion that diabetes could be a main factor in CRS but not in sirenomelia [Bruce et al., 2009]. This does not exclude the possibility that a few cases of sirenomelia may have a pathogenesis linked to maternal diabetes that is similar or identical to that of some CRS cases.

Descriptive Analysis

The infants with sirenomelia were born alive in almost half of the cases which did not undergo ETOPFA, and presented a higher proportion of prematurity and of twinning than expected. These characteristics were the same in both the isolated and MCA case groups.

Associated Defects

The division of infants with sirenomelia into isolated and MCA case groups did not show any epidemiological difference between these two groups other than an association with younger maternal age in the MCA group. The proportion of each defect considered part of the sirenomelia/CRS spectrum was always higher, although not statistically significantly, in the MCA than in the isolated group, suggesting that in the former group the cases were described in more detail. Since only 16% of patients had the limited descriptor of “sirenomelia,” the studied sample of 84% of cases seems appropriate for evaluating the extension of the sirenomelia/CRS spectrum.

Single umbilical artery, lethal renal a/dysgenesis, and oligohydramnios, were described much more frequently in sirenomelia than in CRS non-sirenomelic [Källén and Winberg, 1974; Martínez-Frías et al., 2008]. Nonetheless, only the urinary defects, as well as the genital, and large bowel defects, were described in approximately half of the cases with sirenomelia in our sample. Single or anomalous umbilical artery, as well as defects of the lower spinal column, were described in only 16% of the cases, while oligohydramnion derived defects in 24.9% of the case. The differences in diagnostic methods (clinical examination with or without imaging studies or autopsy) does not explain the observed differences of frequency. However, we could not discard that some defects of this spectrum with wide phenotypic variability were preferentially described in some registries.

Other defects were described in sirenomelia with a frequency similar to that of the lower spinal column defects or single or anomalous umbilical artery frequency. Upper limb defects, mainly pre-axial reduction, congenital heart defect, and central nervous system, mainly spina bifida, occurred in 14.9%, 10.8%, and 10.4% of all cases, respectively, and could be also accepted as part of the sirenomelia/CRS spectrum. Since only cases of sirenomelia were studied here, we cannot assess the prevalence of the abovementioned defects in non-sirenomelic CRS case-series. Therefore, for future work, the observations here reported could only suggest which defects to be included in the sirenomelia spectrum, and which considered as associated defects, that is, not as part of the spectrum.

Several other early defects, such as VATER and twinning, have been linked to sirenomelia/CRS through common risk factors such as maternal diabetes [Zaw and Stone, 2002; Castori et al., 2010] or through the overlapping of the specific defects in each condition [Källén and Winberg, 1974]. From the five defects included in the VATER acronym (Vertebral, Anal atresia, Tracheo-Esophageal, Renal and Radial anomalies), three (VAR) are already part of the accepted sirenomelia/CRS spectrum. Even if we described among our sirenomelia cases 28 with radial defects and 16 with tracheo-esophageal anomalies, only 3 cases presented exclusively defects of the VATER association. Thus the proposition of a unique spectrum for sirenomelia/CRS and VATER [Castori et al., 2010] was not supported by our findings.

Some authors [Heifetz, 1984; Stevenson et al., 1986] which support the vascular “steal” theory for sirenomelia etiology have proposed that single umbilical artery or anomalous umbilical artery were always present in sirenomelia. However, we could not confirm this hypothesis with our findings. Because single umbilical artery is considered a minor defect and not reported by some registries, the frequency we found could very well represent an underestimate. Garrido-Allepuz et al. [2011] have updated the discussion about the two hypotheses about sirenomelia etiology, and pointed that both theories were not mutually exclusive although the deficient blastogenesis hypothesis explains both the vascular and the organs defects.

The frequency of the associations of VRD as those described here, involving sirenomelia with bladder exstrophy, holoprosencephaly/cyclopia, or acardia-acephalus in the same infant is greater than expected considering the prevalence of each one of these defects. Also the association in the same infant of three VRD as sirenomelia, acardia-acephalus, and cyclopia is never expected to occur under random expectations. These associations, the high frequency of twinning, and the overlap of defects with other early conditions as VATER and CRS indicate a common pathway for them. They could be the result of early insults in blastogenesis caused by the primary gene mutation or by environmental determinants or by interaction of both, and the final phenotype will depend on the disease modifying genes, divided in those uniquely affected by the primary mutation, and those whose actions reflect generic responses to organism stress evoked by the principal mutation (intermediate phenotypes). Since each path involves concatenated networks, the application of biological network analysis [Loscalzo et al., 2007], together with molecular results, could help us to understand this class of complex diseases.

CONCLUSIONS

Sirenomelia prevalence was noted to be higher in the Mexican registry (2.36 per 100,000) than in others registries, with no plausible explanation identified based on the available data. Prevalence estimates of sirenomelia around the world were similar otherwise (0.98 per 100,000), with exception of Hungary and Campania-Italy registries where a low prevalence suggests that under-ascertainment could be occurring. The proportion of twinning among cases of sirenomelia was higher than the 1 or 2% expected in the general population. The sirenomelia prevalence was also higher in younger age mothers among all cases and those with MCA, but not among the isolated case. Half of the cases with sirenomelia presented

also with genital, large bowel, and urinary defects. About 10–15% of sirenomelia cases had lower spinal column defects, single or anomalous umbilical artery, upper limb, cardiac, and central nervous system defects. There was a higher than expected association of sirenomelia with other VRD such as bladder exstrophy, cyclopia/holoprosencephaly, and acardia-acephalus. The biological network analysis approach of these related complex conditions was suggested for future work.

Acknowledgments

Grant sponsor: MCT/CNPq, Brazil; Grant numbers: 573993/2008-4, 476978/2008-4, 554755/2009-2, 306750/2009-0, 402045/2010-6; Grant sponsor: FAPERJ, Brazil; Grant numbers: E-26/102.748/2008, E-26/170.007/2008; Grant sponsor: CAPES, Brazil; Grant numbers: 1957/2009, 2799/2010; Grant sponsor: Center for Disease Control and Prevention; Grant number: 1U50DD000524-02.

This study was supported by the MCT/CNPq, Brazil (grant nos. 573993/2008- 4, 476978/2008-4, 554755/2009-2, 306750/2009-0, 402045/2010-6), FAPERJ, Brazil (grant nos. E-26/102.748/2008, E-26/170.007/2008), and CAPES, Brazil (grant nos. 1957/2009, 2799/2010). Work conducted at the Centre of the International Clearinghouse for Birth Defects Surveillance and Research was supported by the Center for Disease Control and Prevention (1U50DD000524-02). This work was in part supported by Instituto de Salud Carlos III (ISCIII, Ministry of Science and Innovation) of Spain, and the Fundación 1000 sobre Defectos Congénitos, of Spain. CIBERER is an initiative of ISCIII. CIBERER is an initiative of ISCIII. Components of ECEMC's Peripheral Group are gratefully acknowledged.

References

Abu-Hijleh G, Qi BQ, Williams AK, Beasley SW. Development of the bones and synovial joints in the rat model of the VATER association. J Orthop Sci. 2000; 5:390–396. [PubMed: 10982690]

Agarwal P, Wylie JN, Galceran J, Arkhitko O, Li C, Deng C, Grosschedl R, Bruneau BG. Tbx5 is essential for forelimb bud initiation following patterning of the limb filed in the mouse embryo. Development. 2003; 130:623–633. [PubMed: 12490567]

Akbayir O, Gungorduk K, Sudolmus S, Gulkilik A, Ark C. First trimester diagnosis of sirenomelia: A case report and review of the literature. Arch Gynecol Obstet. 2008; 278:589–592. [PubMed: 18360750]

Al Kaissi A, Klaushofer K, Grill F. Caudal regression syndrome and popliteal webbing in connection with maternal diabetes mellitus: A case report and literature review. Cases J. 2008; 1/407:1–4.

Al-Haggar M, Yahia S, Abdel-Hadi D, Grill F, Al Kaissi A. Sirenomelia (symelia apus) with Potter's syndrome in connection with gestational diabetes mellitus: A case report and literature review. Afr Health Sci. 2010; 10:395–399. [PubMed: 21416043]

Aslan Y, Erduran E, Kutlu N. Autosomal recessive multiple pterygium syndrome: A new variant? Am J Med Genet. 2000; 93:194–197. [PubMed: 10925380]

Bartsocas CS, Papas CV. Popliteal pterygium syndrome: Evidence for a severe autosomal recessive form. J Med Genet. 1972; 9:222–226. [PubMed: 4339984]

Bianchi, DW.; Crombleholme, TM.; Alton, ME. Sirenomelia. In: Medina, M., editor. Fetology. New York: McGraw Hill; 2000. p. 649-655.

Blaicher W, Lee A, Deutinger J, Bernaschek G. Sirenomelia: Early prenatal diagnosis with combined two- and three-dimensional sonography. Ultrasound Obstet Gynecol. 2001; 17:542–545. [PubMed: 11422982]

Botto LD, Khoury MJ, Mastroiacovo P, Castilla EE, Moore CA, Skjaerven R, Mutchinick OM, Borman B, Cocchi G, Czeizel AE, Goujard J, Irgens LM, Lancaster PAL, Martinez-Frias ML, Merlob P, Ruusinen A, Stoll C, Sumiyoshi Y. The spectrum of congenital anomalies of the VATER association: An international study. Am J Med Genet. 1997; 71:8–15. [PubMed: 9215761]

Bruce JH, Romaguera RL, Rodriguez MM, González-Quintero VH, Azouz EM. Caudal dysplasia syndrome and sirenomelia: Are they part of a spectrum? Fetal Pediatr Pathol. 2009; 28:109–131. [PubMed: 19365740]

Carbillon L, Seince N, Largilliere C, Bucourt M, Uzan M. First trimester diagnosis of sirenomelia: A case report. Fetal Diagn Ther. 2001; 16:284–288. [PubMed: 11509850]

Castilla EE, Mastroiacovo P. Very rare defects: What can we learn? Am J Med Genet Part C. 2011 (this issue).

Castilla EE, Orioli IM. ECLAMC: The Latin American Collaborative Study of Congenital Malformations. Community Genet. 2004; 7:76–94. [PubMed: 15539822]

Castilla EE, Mastroiacovo P, López-Camelo JS, Saldarriaga W, Isaza C, Orioli IM. Sirenomelia and cyclopia cluster in Cali, Colombia. Am J Med Genet Part A. 2008; 146A:2626–2636. [PubMed: 18798307]

Castori M, Rinaldi R, Capocaccia P, Roggini M, Grammatico P. VACTERL association and maternal diabetes: A possible causal relationship? Birth Defects Res A Clin Mol Teratol. 2008; 82:169–172. [PubMed: 18181216]

Castori M, Silvestri E, Cappellacci S, Binni F, Sforzolini GS, Grammatico P. Sirenomelia and VACTERL association in the offspring of a woman with diabetes. Am J Med Genet Part A. 2010; 152A:1803–1807. [PubMed: 20583159]

Collins-Schramm HE, Chima B, Morii T, Wah K, Figueroa Y, Criswell LA, Hanson RL, Knowler WC, Silva G, Belmont JW, Seldin MF. Mexican American ancestry-informative markers: Examination of population structure and marker characteristics in European Americans, Mexican Americans, Amerindians and Asians. Hum Genet. 2004; 114:263–271. [PubMed: 14628215]

Das BB, Rajegowda BK, Bainbridge R, Giampietro PF. Caudal regression syndrome versus sirenomelia: A case report. J Perinatol. 2002; 22:168–170. [PubMed: 11896526]

Dawrant MJ, Giles S, Bannigan J, Puri P. Adriamycin produces a reproducible teratogenic model of vertebral, anal, cardiovascular, tracheal, esophageal, renal, and limb anomalies in the mouse. J Pediatr Surg. 2007; 42:1652–1658. [PubMed: 17923191]

Delissaint D, McKyer ELJ. A systematic review of factors utilized in preconception health behavior research. Health Educ Behav. 2011 Apr 21. Epub ahead of print. 10.1177/1090198110389709

Di Lorenzo M, Brandt ML, Veilleux A. Sirenomelia in an identical twin. J Pediatr Surg. 1991; 26:1334–1336. [PubMed: 1812270]

Duesterhoeft SM, Ernst LM, Siebert JR, Kapur RP. Five cases of caudal regression with an aberrant abdominal umbilical artery: Further support for a caudal regression-sirenomelia spectrum. Am J Med Genet Part A. 2007; 143A:3175–3184. [PubMed: 17963219]

Duhamel B. From the mermaid to the anal imperforation: The syndrome of caudal regression. Arch Dis Child. 1961; 36:152–155. [PubMed: 21032381]

Duncan PA, Shapiro LR. Sirenomelia and VATER association: Possible interrelated disorders with common embryologic pathogenesis. Dysmorph Clin Genet. 1993; 2:96–103.

Duncan PA, Shapiro LR, Klein RM. Sacrococcygeal dysgenesis association. Am J Med Genet. 1991; 41:153–161. [PubMed: 1785625]

Foerster, A. Die Missbildungen des Menschen, nebst einem Atlas (German). Manke: Jena Friedrich; 1861–1865.

García-García MJ, Eggenschwiler JT, Caspary T, Alcorn HL, Wyler MR, Huangfu D, Rakeman AS, Lee JD, Feinberg EH, Timmer JR, Anderson KV. Analysis of mouse embryonic patterning and morphogenesis by forward genetics. Proc Natl Acad Sci USA. 2005; 102:5913–5919. [PubMed: 15755804]

Garrido-Allepuz C, Haro E, González-Lamuño D, Martínez-Frías ML, Bertocchini F, Ros MA. A clinical and experimental overview of sirenomelia: Insight into the mechanisms of congenital limb malformations. Dis Models Mech. 2011; 4:289–299.

Goodlow OG, McCoy Sibley RI, Allen BG, Kamanda WS, Gullattee AC, Rayfield WC. Sirenomelia: Mermaid syndrome. J Natl Med Assoc. 1988; 80:343–346. [PubMed: 3351972]

Guidera KJ, Raney E, Ogden JA, Highhouse M, Habal M. Caudal regression: A review of seven cases, including the mermaid syndrome. J Pediatr Orthop. 1991; 11:743–747. [PubMed: 1960198]

Gurakan B, Karaaslan E, Balci S. Sirenomelia in an infant of a diabetic mother: A case report. Turk J Pediatr. 1996; 38:393–397. [PubMed: 8827914]

Halder A, Pahi J, Chaddha V, Agarwal SS. Sirenomelia sequence associated with craniorachischisis totalis, limb reduction and primitive heart. Indian Pediatr. 2001; 38:1041–1045. [PubMed: 11568383]

Heifetz SA. Single umbilical artery. A statistical analysis of 237 autopsy cases and review of the literature. Perspect Pediatr Pathol. 1984; 8:345–378. [PubMed: 6514541]

Hentschel J, Stierkorb E, Schneider G, Goedde S, Siemer S, Gortner L. Caudal regression sequence: Vascular origin? J Perinatol. 2006; 26:445–447. [PubMed: 16801960]

Hilbelink DR, Kaplan S. Sirenomelia: Analysis in the cadmium- and lead-treated golden hamster. Teratog Carcinog Mutagen. 1986; 6:431–440. [PubMed: 2878508]

Holmes LB. Teratogen-induced limb defects. Am J Med Genet. 2002; 112:297–303. [PubMed: 12357474]

ICBDSR International Clearinghouse for Birth Defects Surveillance and Research. [Nov 27, 2009] Annual Report 2007. 2009. Roma and websitehttp://www.icbdsr.org

Jaiyesimi F, Gomathinayagam T, Dixit A, Amer M. Sirenomelia without vitelline artery steal. Ann Saudi Med. 1998; 18:542–544. [PubMed: 17344743]

Jensen PKA, Hansen P. A bisatellited marker chromosome in an infant with the caudal regression anomalad. Clin Genet. 1981; 19:126–129. [PubMed: 6937274]

Kadian YS, Duhan N, Rattan KN, Rawal M. Sirenomelia (mermaid syndrome): A rare anomaly. Afr J Paediatr Surg. 2008; 5:105–106. [PubMed: 19858681]

Källén B, Winberg J. Caudal mesoderm pattern of anomalies: From renal agenesis to sirenomelia. Teratology. 1974; 9:99–112. [PubMed: 4812361]

Källén B, Castilla EE, Lancaster PAL, Mutchinick O, Knudsen L, Martinez-Frias ML, Mastroiacovo P, Robert E. The cyclops and the mermaid. An epidemiological study of two types of rare malformations. J Med Genet. 1992; 29:30–35. [PubMed: 1552541]

Kalter H. Case reports of malformations associated with maternal diabetes: History and critique. Clin Genet. 1993; 43:174–179. [PubMed: 8330451]

Kampmeier OF. On sireniform monsters, with a consideration of the causation and the predominance of the male sex among them. Anat Rec. 1927; 34:365–389.

Kibar Z, Torban E, McDearmid JR, Reynolds A, Berghout J, Mathieu M, Kirillova I, De Marco P, Merello E, Hayes JM, Wallingford JB, Drapeau P, Capra V, Gros P. Mutations in VANGL1 associated with neural-tube defects. N Engl J Med. 2007; 356:1432–1437. [PubMed: 17409324]

Kjaer KW, Keeling JW, Opitz JM, Gilbert-Barness E, Hartling U, Hansen BF, Kjær I. Sirenomelia sequence according to the distance between the first sacral vertebra and the ilia. Am J Med Genet Part A. 2003; 120A:503–508. [PubMed: 12884429]

Köchling J, Karbasiyan M, Reis A. Spectrum of mutations and genotype-phenotype analysis in Currarino syndrome. Eur J Hum Genet. 2001; 9:599–605. [PubMed: 11528505]

Langer B, Stoll C, Nicolav R, Gasser B, Schlaedr G. Sirenomelia and situs inversus: Case report and review of the literature. Fetal Diagn Ther. 1999; 11:79–84. [PubMed: 8719727]

Larsen, WJ. Chapter 11: Development of the limbs. New York: Churchill Livingstone; 1993. Human embryology; p. 281-307.

Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. Diabetes Care. 2008; 31:899–904. [PubMed: 18223030]

Loscalzo J, Kohane I, Barabasi AL. Human disease classification in the postgenomic era: a complex systems approach to human pathobiology. Mol Syst Biol. 2007; 3:124. [PubMed: 17625512]

Lowry RB, Sibbalda B, Bedarda T. Stability of prevalence rates of anorectal malformations in the Alberta Congenital Anomalies Surveillance System 1990–2004. J Pediatr Surg. 2007; 42:1417–1421. [PubMed: 17706507]

Lynch SA, Wright C. Sirenomelia, limb reduction defects, cardiovascular malformation, renal agenesis in an infant born to a diabetic mother. Clin Dysmorphol. 1997; 6:75–80. [PubMed: 9018422]

Martínez-Frías ML. Epidemiology of acephalus/acardius monozygotic twins: New insights into an epigenetic causal hypothesis. Am J Med Genet Part A. 2009; 149A:640–649. [PubMed: 19291778]

Martínez-Frías ML, Bermejo E, Rodriguez-Pinilla E, Prieto L, Frias JL. Epidemiological analysis of outcomes of pregnancy in gestational diabetic mothers. Am J Med Genet. 1998a; 78:140–145. [PubMed: 9674904]

Martínez-Frías ML, Garcia A, Bermejo E. Cyclopia and sirenomelia in a liveborn infant [letter]. J Med Genet. 1998b; 35:263–264. [PubMed: 9541120]

Martínez-Frías ML, Bermejo E, Rodriguez-Pinilla E, Prieto L. ECEMC Working Group. Does Single Umbilical Artery (SUA) Predict Any Type of Congenital Defect? Clinical–Epidemiological Analysis of a Large Consecutive Series of Malformed Infants. Am J Med Genet Part A. 2008; 146A:15–25. [PubMed: 17999408]

Messineo A, Innocenti M, Gelli R, Pancani S, Lo Piccolo R, Martin A. Multidisciplinary surgical approach to a surviving infant with sirenomelia. Pediatrics. 2006; 118:e220–e223. [PubMed: 16801393]

Murphy JJ, Fraser GC, Blair GK. Sirenomelia: Case of the surviving mermaid. J Pediatr Surg. 1992; 27:1265–1268. [PubMed: 1403499]

O'Railly R, Müller F. Interpretation of some median anomalies as illustrated by cyclopia and symmelia. Teratology. 1989; 40:409–421. [PubMed: 2623629]

Opitz JM, Zanni G, Reynolds JF Jr, Gilbert-Barness E. Defects of blastogenesis. Am J Med Genet. 2002; 115:269–286. [PubMed: 12503120]

Orioli IM, Mastroiacovo P, López-Camelo JS, Saldarriaga W, Isaza C, Aiello H, Zarante I, Castilla EE. Clusters of sirenomelia in South America. Birth Defect Res A. 2009; 85:112–118.

Ouimette JF, Jolin ML, L'honoré A, Gifuni A, Drouin J. Divergent transcriptional activities determine limb identity. Nat Commun. 2010; 1:35–43. [PubMed: 20975709]

Padmanabhan R. Retinoic acid-induced caudal regression syndrome in the mouse fetus. Reprod Toxicol. 1998; 12:139–151. [PubMed: 9535508]

Patel S, Suchet I. The role of color and power Doppler ultrasound in the prenatal diagnosis of sirenomelia. Ultrasound Obstet Gynecol. 2004; 24:684–691. [PubMed: 15517539]

Pennimpede T, Cameron DA, MacLean GA, Li H, Abu-Abed S, Petkovich M. The role of CYP26 enzymes in defining appropriate retinoic acid exposure during embryogenesis. Birth Defects Res A Clin Mol Teratol. 2010; 88:883–894. [PubMed: 20842651]

Rittler M, Paz JE, Castilla EE. VACTERL association, epidemiologic definition and delineation. Am J Med Genet. 1996; 63:529–536. [PubMed: 8826430]

Rougemont AL, Bouron-Dal Soglio D, Désilets V, Jovanovic M, Perreault G, Laurier Oligny L, Fournet JC. Caudal dysgenesis, sirenomelia, and situs inversus totalis: A primitive defect in blastogenesis. Am J Med Genet Part A. 2008; 146A:1470–1476. [PubMed: 18470923]

Sarpong S, Headings V. Sirenomelia accompanying exposure of the embryo to cocaine. South Med J. 1992; 85:545–547. [PubMed: 1585209]

Savader SJ, Savader BL, Clark RA. Sirenomelia without Potter syndrome: MR characteristics. J Comput Assist Tomogr. 1989; 13:689–691. [PubMed: 2745791]

Scheidel, W. Demography of the ancient world. In: Durlauf, SN.; Blume, LE., editors. The new Palgrave dictionary of economics online. Palgrave Macmillan; 2008.

Schiesser M, Holzgreve W, Lapaire O, Willi N, Lüthi H, Lopez R, Tercanli S. Sirenomelia, the mermaid syndrome—Detection in the first trimester. Prenatl Diagn. 2003; 23:493–495.

Schüler L, Salzano FM. Patterns in multi-malformed babies and the question of the relationship between sirenomelia and VAC-TERL. Am J Med Genet. 1994; 49:29–35. [PubMed: 8172248]

Selig AM, Benacerraf B, Greene MF, Garber M-F, Genest DR. Renal dysplasia, megalocystis, and sirenomelia in four siblings. Teratology. 1993; 47:65–71. [PubMed: 8475459]

Stahl A, Tourame P. De la tératologie aux monstres de la mythologie et des le gendes antiques (From teratology to mythology: Ancient legends). Arch Pédiatr. 2010; 17:1716–1724. [French]. [PubMed: 21074387]

Stanton MP, Penington EC, Hutson JM. A surviving infant with sirenomelia (Mermaid syndrome) associated with absent bladder. J Pediatr Surg. 2003; 38:1266–1268. [PubMed: 12891511]

StataCorp. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP; 2007.

Stevenson, RE. Limbs. In: Stevenson, RE.; Hall, JG., editors. Human malformations and related anomalies. 2. New York: Oxford University Press; 2006.

Stevenson RE, Jones KL, Phelan MC, Jones MC, Barr M Jr, Clericuzio C, Harley RA, Benirschke K. Vascular steal: The pathogenetic mechanism producing sirenomelia and associated defects of the viscera and soft tissues. Pediatrics. 1986; 78:451–457. [PubMed: 3748679]

Stocker J, Heifetz S. Sirenomelia, a morphological study of 33 cases and review of the literature. Perspect Pediatr Pathol. 1987; 10:7–50. [PubMed: 3588246]

Taghavi MM, Jafari Naveh HR, Shariati M, Morteza Zade F. Sirenomelia (mermaid syndrome): An infant from parents who used a special form of snuff. Pak J Biol Sci. 2009; 12:722–725. [PubMed: 19634478]

Thottungal AD, Charles AK, Dickinson JE, Bower C. Caudal dysgenesis and sirenomelia-single centre experience suggests common pathogenic basis. Am J Med Genet Part A. 2010; 152A:2578–2587. [PubMed: 20734338]

Valenzano M, Paoletti R, Rossi A, Farinini D, Garslaschi G, Fulcheri E. Sirenomelia. Pathological features, antenatal ultrasono-graphic clues, and a review of current embryogenic theories. Hum Reprod Update. 1999; 5:82–88. [PubMed: 10333372]

Vargas FR, Roessler E, Gaudenz K, Belloni E, Whitehead AS, Kirke PN, Mills JL, Hooper G, Stevenson RE, Cordeiro I, Correia P, Felix T, Gereige R, Cunningham ML, Canún S, Antonarakis SE, Strachan T, Tsui LC, Scherer SW, Muenke M. Analysis of the human Sonic Hedgehog coding and promoter regions in sacral agenesis, tripha-langeal thumb, and mirror polydactyly. Hum Genet. 1998; 102:387–392. [PubMed: 9600232]

Wasnik A, Lalchandani UR. Sirenomelia—Sympus uni pus (mermaid deformity). Pediatr Radiol. 2010; 40:S14. [PubMed: 20706712]

Wei X, Sulik KK. Pathogenesis of caudal dysgenesis/sirenomelia induced by ochratoxin A in chick embryos. Teratology. 1996; 53:378–391. [PubMed: 8910984]

Zakin L, De Robertis EM. Inactivation of mouse twisted gastrulation reveals its role in promoting Bmp4 activity during forebrain development. Development. 2004; 131:413–424. [PubMed: 14681194]

Zakin L, Reversade B, Kuroda H, Lyons KM, De Robertis EM. Sirenomelia in Bmp7 and Tsg compound mutant mice: Requirement for Bmp signaling in the development of ventral posterior mesoderm. Development. 2005; 132:2489–2499. [PubMed: 15843411]

Zanforlin Filho SM, Guimarães Filho HA, Araujo E Jr, Pires CR, Mattar R, Nardozza LM. Sirenomelia sequence: Early prenatal diagnosis of one rare case associated with acardiac malformation. Arch Gynecol Obstet. 2007; 275:315–316. [PubMed: 16983560]

Zaw W, Stone DG. Caudal regression syndrome in twin pregnancy with type II diabetes. J Perinatol. 2002; 22:171–174. [PubMed: 11896527]

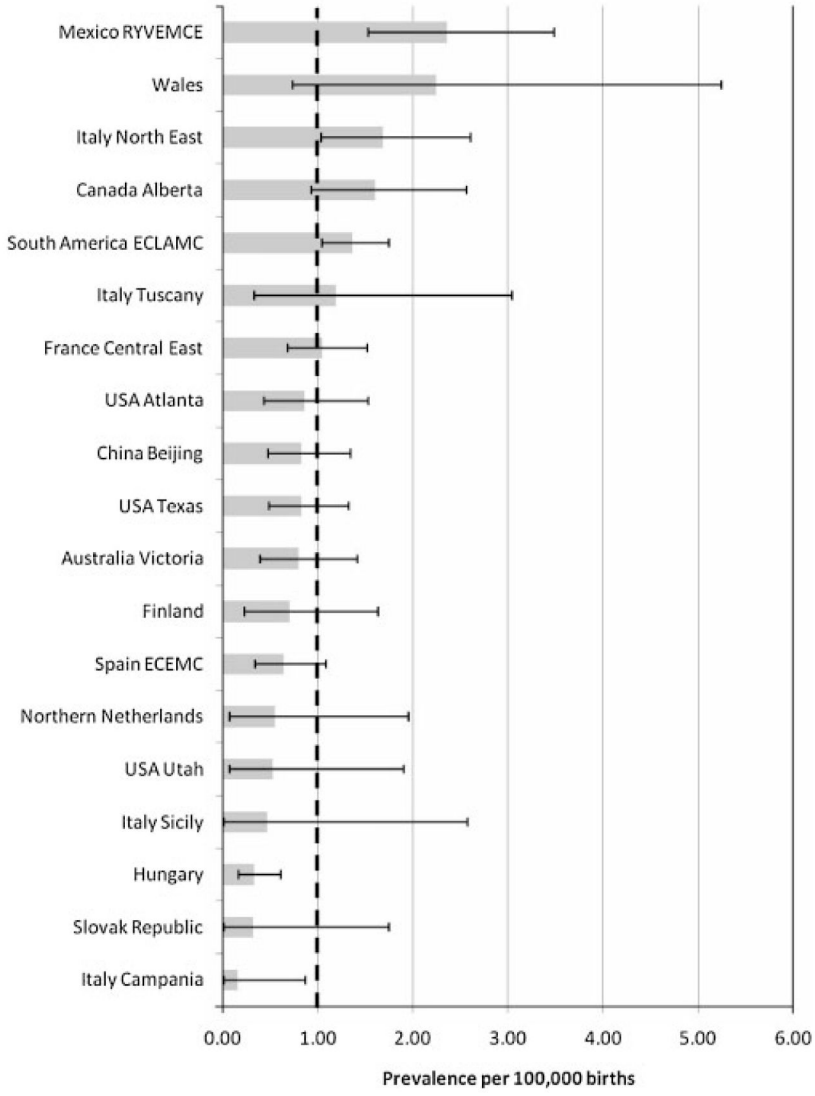

Figure 1.

Total prevalence per 100,000 births (bar) and 95% confidence interval (line) by surveillance program and overall (dotted line) of sirenomelia in 19 surveillance programs members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).

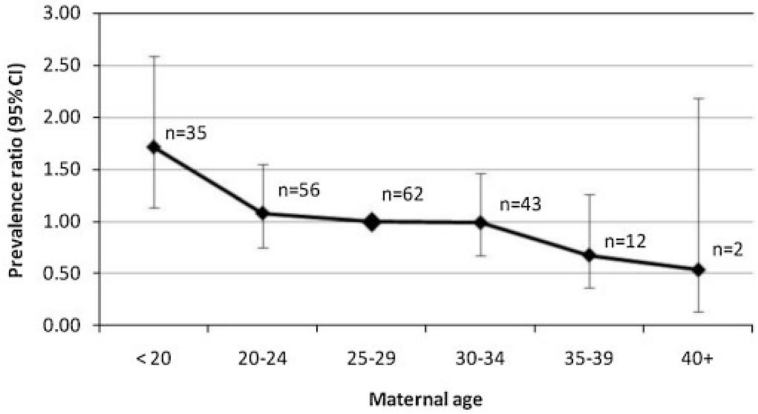

Figure 2.

Prevalence ratios for maternal age groups relative to the reference age group of 25–29 years with corresponding 95% confidence intervals for sirenomelia in 19 surveillance program members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).

TABLE I

Total Prevalence (per 100,000 Births) of Sirenomelia in 19 Surveillance Programs Members of the International Clearinghouse for Birth Defects Surveillance and Research

Surveillance program	Period	Births	Total cases	% of ETOPFA cases	Prevalence (per 100,000 births)	95% Confidence intervals (CI)
Canada Alberta	1980–2005	1,062,483	17	35.3	1.60	0.93–2.56
USA Utah	1997–2004	380,706	2	50.0	0.53	0.06–1.90
USA Atlanta	1968–2004	1,283,999	11	36.4	0.86	0.43–1.53
USA Texas	1996–2002	2,054,788	17	23.5	0.83	0.48–1.32
Mexico RYVEMCE	1978–2005	1,058,885	25	NP	2.36	1.53–3.49
South America ECLAMC	1982–2006	4,556,173	62	NP	1.36	1.04–1.74
Finland	1993–2004	713,494	5	60.0	0.70	0.23–1.64
Wales	1998–2004	222,309	5	80.0	2.25	0.73–5.25
Northern Netherlands	1981–2003	369,658	2	50.0	0.54	0.07–1.95
Slovak Republic	2000–2005	318,257	1	0	0.31	0.01–1.75
Hungary	1980–2005	3,022,194	10	10.0	0.33	0.16–0.61
France Central East	1979–2004	2,500,214	26	88.5	1.04	0.68–1.52
Italy North East	1981–2004	1,186,497	20	35.0	1.69	1.03–2.60
Italy Tuscany	1992–2004	336,744	4	50.0	1.19	0.32–3.04
Italy Campania	1992–2004	643,962	1	100	0.16	0.00–0.87
Italy Sicily	1991–2002	216,257	1	0	0.46	0.01–2.58
Spain ECEMC	1980–2004	2,045,751	13	NR	0.64	0.34–1.09
China Beijing	1992–2005	1,927,622	16	NR	0.83	0.47–1.35
Australia Victoria	1983–2004	1,390,179	11	36.4	0.79	0.39–1.42
		25,290,172	249	24.5[a]	0.98	0.87–1.11

RYVEMCE, Registroy Vigilancia Epidemiológica de Malformaciones Congénitas; ECLAMC, Estudo Colaborativo Latino Americano de Malformações Congênitas; ECEMC, Spanish Collaborative Study of Congenital Malformations; ETOPFA, elective termination of pregnancy for fetal anomaly; NP, not permitted; NR, not reported.

[a]The percentage computed on the 15 surveillance programs registering ETOPFA is 49.5% (n =61/133).

TABLE II

Number of Births, Number of Cases Crude Prevalence Estimates, and Prevalence Ratios for Maternal Age Groups Relative to the Reference Age Group of 25–29 Years for Sirenomelia

Maternal age group	Births[a]	Cases[a]	Prevalence (per 100.000 births)	95% CI	Prevalence ratio	95% CI
<20	2,334,023	35	1.50	1.04–2.09	1.71	1.13–2.59
20–24	5,922,300	56	0.95	0.71–1.23	1.08	0.75–1.55
25–29	7,079,853	62	0.88	0.67–1.12	1.00	(Reference)
30–34	4,966,752	43	0.87	0.63–1.17	0.99	0.67–1.46
35–39	2,024,166	12	0.59	0.31–1.04	0.68	0.36–1.26
40 or older	426,799	2	0.47	0.06–1.69	0.54	0.13–2.19

[a]Cases and births excluded: China before 1997 and after 2003, Italy North East, Italy Sicily because no births by maternal age were available.

TABLE III

Number of Births, Number of Cases, Crude Prevalence Estimates, and Prevalence Ratios for Maternal Age Groups Relative to the Reference Age Group of 25–29 Years for Isolated and MCA Sirenomelia

Maternal age group	Births[a]	Cases[a]	Prevalence (per 100,000 births)	95% CI	Prevalence ratio	95% CI
Isolated						
<20	2,334,023	15	0.64	0.36–1.06	1.26	0.69–2.31
20–24	5,922,300	24	0.41	0.26–0.60	0.80	0.48–1.34
25–29	7,079,853	36	0.51	0.36–0.70	1.00	(Reference)
30–34	4,966,752	24	0.48	0.31–0.72	0.95	0.57–1.59
35–39	2,024,166	5	0.25	0.08–0.58	0.49	0.19–1.24
40 or older	426,799	2	0.47	0.06–1.69	0.92	0.22–3.83
MCA						
<20	2,334,023	20	0.86	0.52–1.32	2.33	1.30–4.18
20–24	5,922,300	32	0.54	0.37–0.76	1.47	0.88–2.47
25–29	7,079,853	26	0.37	0.24–0.54	1.00	(Reference)
30–34	4,966,752	19	0.38	0.23–0.60	1.04	0.58–1.88
35–39	2,024,166	7	0.35	0.14–0.71	0.94	0.41–2.17
40 or older	426,799	0	0.00	0.00–0.86	0.00	NC

MCA, multiple congenital anomalies; NC, not computable.

[a]Cases and births excluded: China before 1997 and after 2003, Italy North East, Italy Sicily because no births by maternal age were available.

TABLE IV

Characteristics of the Infants With Sirenomelia

	Total cases (n = 249)		Isolated cases (n = 123)		Cases with associated malformations (n =126)	
	n	%	n	%	n	%
Sex						
Male	51	20.5	22	17.9	29	23.0
Female	54	21.7	22	17.9	32	25.4
Indeterminate	117	47.0	61	49.6	56	44.4
Missing data	27	10.8	18	14.6	9	7.1
Outcome						
Livebirths	117	47.0	60	48.8	57	45.2
Stillbirths	71	28.5	38	30.9	33	26.2
ETOPFA	61	24.5	25	20.3	36	28.6
Missing data	0	0.0	0	0.0	0	0.0
Birth weight (g)[a]						
<1,500	46	39.3	21	35.0	25	43.9
1,500–2,500	51	43.6	31	51.7	20	35.1
>2,500	13	11.1	5	8.3	8	14.0
Missing data	7	6.0	3	5.0	4	7.0
Gestational age (week)[a]						
<32	30	25.6	14	23.3	16	28.1
33–36	44	37.6	22	36.7	22	38.6
≥ 37	30	25.6	18	30.0	12	21.1
Missing data	13	11.1	6	10.0	7	12.3
Parity						
0	39	15.7	16	13.0	23	18.3
1	87	34.9	49	39.8	38	30.2
2 or more	35	14.1	17	13.8	18	14.3
Missing data	88	35.3	41	33.3	47	37.3
Previous spontaneous abortions						
0	74	29.7	40	32.5	34	27.0

	Total cases (n = 249)		Isolated cases (n = 123)		Cases with associated malformations (n =126)	
	n	%	n	%	n	%
1	16	6.4	7	5.7	9	7.1
Missing data	159	63.9	76	61.8	83	65.9
Plurality						
Single	204	81.9	101	82.1	103	81.7
Twin	20	8.0	11	8.9	9	7.1
Triplet	1	0.4	0	0.0	1	0.8
Missing data	24	9.6	11	8.9	13	10.3
Maternal age						
<20	35	14.1	15	12.2	20	15.9
20–24	62	24.9	27	22.0	35	27.8
25–29	64	25.7	37	30.1	27	21.4
30–34	44	17.7	25	20.3	19	15.1
≥35	14	5.6	7	5.7	7	5.6
Missing data	30	12.0	12	9.8	18	14.3
Parental age difference						
Mother same age or older	25	10.0	12	9.8	13	10.3
Mother 1–2 years younger	20	8.0	8	6.5	12	9.5
Mother 3–4 years younger	13	5.2	8	6.5	5	4.0
Mother >4 years younger	19	7.6	11	8.9	8	6.3
Missing data	172	69.1	84	68.3	88	69.8
Maternal education (years)						
<9	21	8.4	15	12.2	6	4.8
9 or more	37	14.9	17	13.8	20	15.9
Missing data	191	76.7	91	74.0	100	79.4

[a]Birth weight, gestational age: the data are for livebirths only.