

Prenatal prevalence of skeletal dysplasias and a proposal ultrasonographic diagnosis approach

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ABSTRACT

Objective. To determine the prevalence of fetal bone dysplasias diagnosed at the Department of Maternal Fetal Medicine (UNIMEF) of the Instituto Nacional de Perinatología (INPer); and to describe the most frequent skeletal dysplasias and to propose a diagnostic flow chart. **Materials and methods.** This is a case series study including skeletal dysplasias cases from January 1995 until December 2009 at the UNIMEF. Statistical analysis was performed using SPSS 12 statistical software. **Results.** A total of 81,892 births were registered at the institution during the study period. The prevalence of bone dysplasia was 8.1 per 10,000 births. We used a diagnostic flow chart that was developed at our institution to diagnose skeletal dysplasias. Micromelia (n = 40, 59.7%) and both rhizomelia and mesomelia (n = 17, 25.3%) were highly prevalent. We found other structural anomalies in 40 cases (61.1%), which were associated with different skeletal dysplasias; these other anomalies were mainly congenital heart diseases (12 cases) with a predominance of ventricular septal defects. There was polyhydramnios in 43.2% of cases. The mean of the gestational age at diagnosis was 24.5 weeks (SD 5.66). The karyotype was obtained in 11.9% (8/67) of cases. A total of 7 stillbirths and 11 neonatal deaths were registered, of which only 10 cases received a necropsy. Births occurred in the third trimester for 88% of cases, of which 85% were born via Cesarean section, whereas in the second trimester, the vaginal approach was chosen in 100% of cases. **Conclusions.** The prenatal diagnosis of bone dysplasias is challenging due to the late development of the diagnostic features. Nevertheless, using ultrasonography in a systematic approach, in conjunction with a multidisciplinary approach, is a key factor in the diagnosis of this disease during the fetal period.

Prevalencia prenatal de displasia esquelética y una propuesta de diagnóstico ultrasonográfico

RESUMEN

Objetivo. Determinar la prevalencia de displasia esquelética fetal evaluada en la Unidad de Investigación del Departamento de Medicina Fetal (UNIMEF) del Instituto Nacional de Perinatología Isidro Espinosa de los Reyes (INPer); describir la más frecuente y proponer un flujograma de abordaje diagnóstico. **Material y métodos.** Se realizó un estudio de serie de casos de enero de 1995 a diciembre 2009, se incluyeron todos los casos con diagnóstico inicial de displasia esquelética evaluados en la UNIMEF. El análisis estadístico se realizó con el programa SPSS 12. **Resultados.** Se incluyeron un total de 67 casos de displasias esqueléticas fetales diagnosticadas en la UNIMEF. En el periodo de estudio se registraron 81,892 nacimientos, prevalencia de 8.1 por cada 10,000 nacidos vivos (67 casos). Se usó un flujograma diagnóstico elaborado y utilizado en el Departamento de Medicina Fetal para el abordaje de las displasias esqueléticas. Las alteraciones esqueléticas diagnosticadas por ultrasonografía en la etapa prenatal se comportaron de la siguiente manera: micromelia en 59.7% (40/67), rizomelia o mesomelia 25.3% (17/67). En 40 casos (61.1%) se encontraron anomalías estructurales asociadas, diferentes a la displasia esquelética, principalmente las cardiopatías en 12 casos predominando la comunicación interventricular. En 43.2% (29/67) la displasia esquelética se acompañó de polihidramnios. La edad gestacional a la que se realizó el diagnóstico tuvo una media de 24.5 semanas de gestación \pm 5.66. El cariotipo se realizó en tan solo 11.9% (8/67) de los casos. Se presentaron un total de siete óbitos y 11 muertes neonatales, sólo en diez casos se realizó necropsia. La resolución del embarazo se dio en el tercer trimestre en 88% de los casos (59/67); de éstos, 85% (51/59) fue por vía abdominal. En el segundo trimestre la resolución se dio por vía vaginal en 100% de los casos en los diez nacimientos presentados (14%). **Conclusiones.** El diagnóstico prenatal de displasia esquelética constituye un reto,

Key words. Ultrasound. Bone dysplasias. Prevalence. Prenatal diagnosis.

INTRODUCTION

Bone dysplasias are a wide and heterogeneous group of genetic disorders that are characterized by bone anomalies in morphology, growth or integrity with different inheritance patterns, presentation, natural history and prognosis.¹⁻³ The prevalence of skeletal dysplasias at birth has been estimated at 2.4/10,000 births.^{4,5}

The classification of bone dysplasias, as defined in the 2007 publication "Nosology and Classification of Genetic Skeletal Disorders",³ includes 372 different alterations divided into 37 groups based on molecular, biochemical and radiologic criteria. Of these conditions, 215 conditions are associated with one or more of 140 different genes.

The fetal skeleton can be reliably evaluated by two-dimensional (2D) ultrasound starting at 14 weeks. Ultrasonographic femoral and humeral evaluations are critical during the second half of pregnancy.

Any fetus with tubular bones whose length is inferior to the 5th percentile or below 2 standard deviations for the corresponding gestational age during the second trimester must be evaluated by experts in the field in order to obtain a more precise diagnosis.⁵

In addition to the bone evaluation, other parameters must be considered, such as facial profile (frontal prominence, depressed nasal bridge, micrognathia), presence or flattening of vertebral bodies and hand and feet morphology (polydactyly, adactyly, and finger malformations). It is also very important to screen for signs of lethality, such as micromelia, abdominal circumference/femoral length ratio < 0.16, thoracic circumference below the 5th percentile, thoracic/abdominal circumference < 0.6 and cardiac circumference/thoracic circumference > 0.6.⁶

When abnormalities in other organs are also detected, an increase in morbidity and mortality can be expected. Of note, the precise diagnosis in bone dysplasias reaches nearly 40%.^{7,8} Therefore, it is of utmost importance that the prenatal ultrasound

dado que la integración diagnóstica definitiva en la mayoría de los casos se completa al nacimiento; sin embargo, la evaluación ultrasonográfica sistemática en conjunto con el abordaje multidisciplinario son determinantes en el diagnóstico de esta patología en su etapa fetal.

Palabras clave. Ultrasonido. Displasias esqueléticas. Prevalencia. Diagnóstico prenatal.

diagnosis is made by an expert in morphological ultrasound.

MATERIAL AND METHODS

This was a case series study. We reviewed charts of patients seen at the Department of Maternal Fetal Medicine of the National Institute of Perinatal Medicine, according to institutional admission criteria. Patients with ultrasonography level results and data suggestive of structural bone alterations were included.

The prenatal diagnosis, which confirmed or excluded structural bone alterations, included an evaluation of the different components of the fetal skeleton, including abnormalities in growth, shape, size, texture (bone mineralization and remodeling) and the number and presence of associated anomalies.

All diagnostic tests were performed by maternal-fetal medicine specialists utilizing any of the following equipment: an ultramark 9 HDI with a 3.5 MHz abdominal transducer, a Philips ATL HDI5000 with a 5.2 multifrequency abdominal transducer or a General Electric Voluson 730 Expert. The bone structural evaluation in all suspicious cases required an additional evaluation, which took 30 to 40 min.

Given the presumptive diagnosis of fetal skeletal dysplasia, the cases were discussed in a multidisciplinary section by the Maternal-Fetal, Genetics, Psychology and Social Work Departments. Parents were counseled on diagnostic methods (invasive and non-invasive), treatment options and the follow-up required for each case.

During the ultrasonographic follow-up, we evaluated growth curves, lethality criteria, associated anomalies, delivery method and any additional studies performed on the neonate or stillborn infant.

RESULTS

A total of 81,892 births occurred between January 1995 and December 2009, with 67 cases of fetal

bone dysplasias, resulting in a prevalence of 8.1 per 10,000 newborns per year (Table 1).

The most common skeletal dysplasias in our study were: osteogenesis imperfecta (MIM 166210) (OI) followed by achondroplasia (MIM 100800) and thanatophoric dysplasia (MIM 187600). Femoral hypoplasia, xiphomelic dysplasia, Apert syndrome (MIM 101200) and pelvic hemiatrophy were each diagnosed once, and skeletal dysplasias without a specific diagnosis occurred in 21.8% (15/67) of patients (Figure 1 and Table 2).

The main non-lethal bone dysplasia was achondroplasia (MIM 100800) (13.4%), whereas the most common lethal one was OI type II (20.8%).

The gestational age at the time of diagnosis varied between 13.2 and 38.4 weeks of gestation (median 24.5 ± 5.66 weeks). Diagnoses were made in the second trimester in 46.33% of cases and in the third trimester in 49.2% of cases.

The sonographic markers of skeletal dysplasias identified were: a femur with pronounced curvature ($n = 40$, 59.7%), a decrease in bone density and changes in the cardiothoracic index ($n = 21$ each, 31.3%), a shortening of tubular bones ($n = 20$,

29.8%) and a frontal prominence ($n = 14$, 20.8%) (Figures 2 and 3).

The most representative anomalies were craniosynostosis and frontal prominences in 27 cases (40.2%). Spinal alterations were present in 4 cases (5.9%). Extremities alterations with micromelia occurred in 40 cases (59.7%), and either rhizomelia or mesomelia occurred in 17 cases (25.3%). Finger abnormalities were present in 5 cases. In 40 cases, abnormalities other than bone dysplasia were found, with cardiopathy (specifically interventricular and interauricular septum defects) being the most common (30%), such as an expected finding in this kind of pathology. Abnormal amniotic fluid was found in 29 cases (61.1%), polyhydramnios was present in 43.2% of cases, oligohydramnios was present in 11 cases and there was 1 case of anhydramnios (Table 1).

Nine cases of achondroplasia type skeletal dysplasias were detected. In three of these patients, there was a positive family history. In the first case, both parents were affected (heterozygous for gen FGFR3 mutation), and the infant was diagnosed at 16 weeks of gestational age with severe short extremities, was born at 36 weeks and experienced early neonatal death. In the second case, the parents had a live daughter with achondroplasia (both parents affected), in whom the diagnosis was made at 26.4 weeks of gestation; the daughter was born alive at 30.6 weeks but suffered early neonatal death. In the third case, the parents (mother affected) had a female affected newborn who died at 6 months of age due to pneumonia, and the diagnosis was made at 22.1 weeks of gestation.

Regarding OI, only one case had a direct family history in which the maternal grandmother, mother

Table 1. Affected structures in fetuses with bone dysplasia diagnosis.

Bone abnormality	Number (%)
Cranial	1 (1.5)
Cranial and extremities	26 (38.8)
Spine	2 (3)
Spine and extremities	2 (3)
Extremities	36 (53.7)
Total	67 (100)

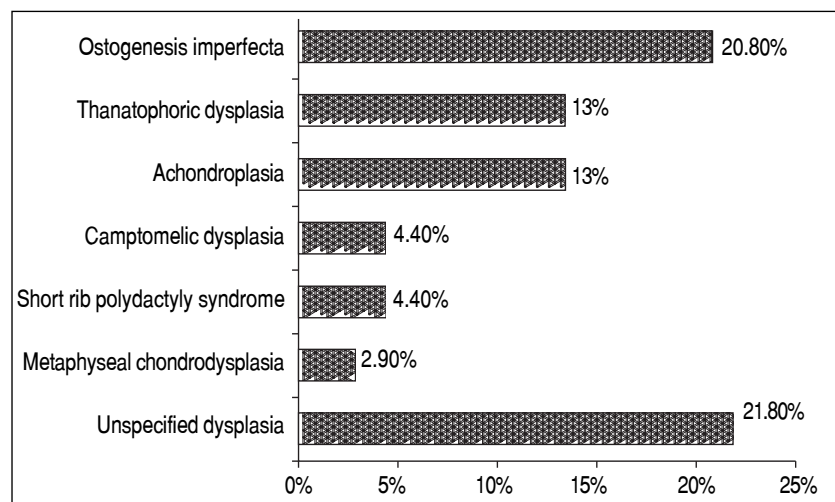


Figure 1. Prenatal diagnosis and frequency of bone dysplasia.

Table 2. Ultrasonographic diagnosis of bone dysplasia in conjunction with clinical (genetic) and necroscopic confirmation.

Ultrasound diagnosis (MIM, n)	Prenatal, n (%)	Necropsy		Clinical evaluated		Integral diagnosis	
		Yes	No	Yes	No	Yes	No
Osteogenesis imperfecta (166210)	14 (20.8)	0	14	14	0	11	3
Achondroplasia (100800)	9 (13.4)	0	9	9	0	9	0
Thanatophoric dysplasia (187600)	9 (13.4)	4	5	9	0	7	2
Campomelic dysplasia (114290)	3 (4.5)	0	3	3	0	2	1
Short rib polydactyly syndrome (263510)	3 (4.5)	2	1	2	1	2	1
Metaphyseal chondrodysplasia (156500)	2 (3)	0	2	2	0	1	1
Achondrogenesis (200600)	2 (3)	2	0	2	0	1	1
Hypochondroplasia (146000)	2 (3)	0	2	2	0	1	1
Pfeiffer syndrome (101600)	2 (3)	0	2	2	0	2	0
Spondylocostal dysostosis (277300)	2 (3)	0	2	2	0	1	1
Femoral hypoplasia	1 (1.5)	0	1	0	1	0	1
Xyphomelic dysplasia	1 (1.5)	0	1	0	1	0	1
Apert syndrome (101200)	1 (1.5)	0	1	0	1	0	1
Pelvic limb hemihypertrophy	1 (1.5)	0	1	0	1	0	1
Unspecified skeletal dysplasia	15 (22.4)	2	13	5	10	5	10
Total	67 (100)	10	57	52	15	42	25

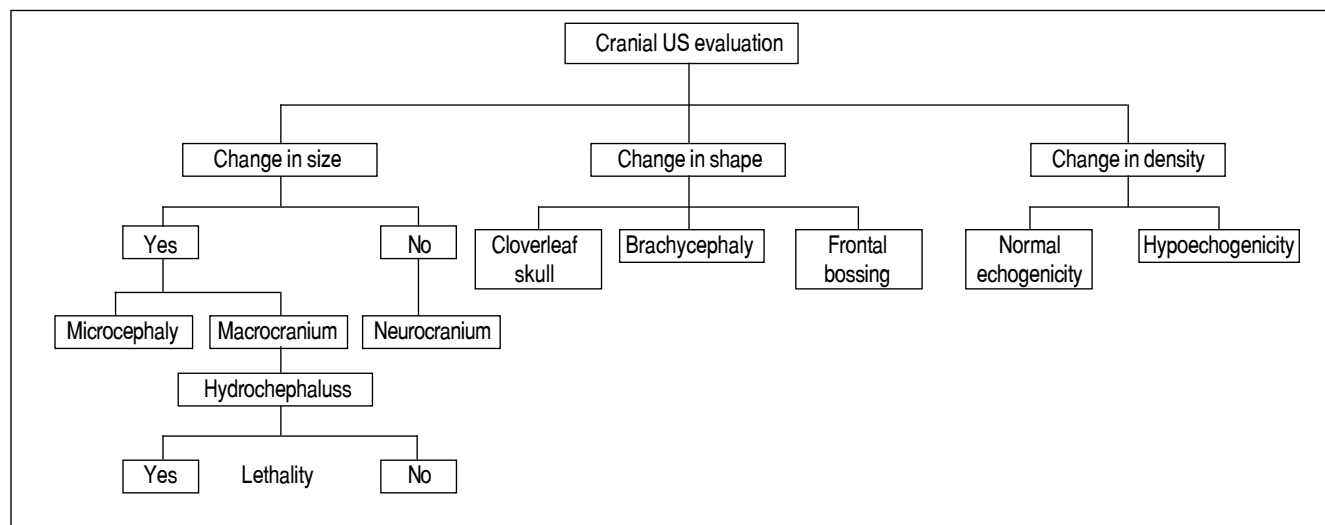


Figure 2. The diagnostic approach for evaluation cranial bone dysplasias.

and brother were diagnosed with OI (type unknown); in this case, the fetus was diagnosed with OI type IV. Of the nine cases of thanatophoric dysplasia, only one case (11.1%) had a family history of it (skeletal dysplasia different to thanatophoric in a second degree relative). When analyzing the total cases of skeletal dysplasia (67), only 5.8% of them had a family history of skeletal dysplasia or any other birth defect.

Karyotyping was performed only in those fetuses with suspected chromosomal alteration, it was performed in 11.9% (7/67) of cases. The results of the karyotype of the seven cases with fetal skeletal

dysplasia were 46, XX (4/7, 57%), 46, XY (3/7, 43%).

Regarding perinatal outcomes, a total of 7 stillbirth and 11 early neonatal deaths accounted for 26.8% of the infants. Neonatal deaths were found in 9.0% (1/11) of cases diagnosed with achondrogenesis, 36.3% (4/11) of cases diagnosed with thanatophoric dysplasia and 54.5% (6/11) (Figure 4) of the unspecified skeletal dysplasia cases.

Anatomopathological studies were performed in 45.4% (5/11) of early neonatal deaths, reaching a comprehensive classification diagnosis in only 70% of them. The Genetics Department reviewed 77% of

cases (52/67) and integrated (clinical, radiologic and pathologic when possible) was performed in 94% of cases (Table 2). For the 6% of cases in which the analysis was not complete, these analyses were not performed due to incompletely described necropsies, lack of assistance of genetics department during the postnatal consultation (deliver occurs in weekend or during night) and incomplete clinical records.

In this study we found a concordance in the prenatal and integrated postnatal diagnosis of 68% (46/67), in 62% (42/67) with the complete postnatal integrated protocol of diagnosis (genetics evaluation, necropsy when possible, neonatologist evaluation) and 6% (4/67) without the complete protocol, in the remaining 32% (21/67) the diagnosis of skeletal dysplasia was confirmed but not the specific diagnosis suspected in the prenatal evaluation.

The mean of gestational age at birth was 36.3 ± 6.33 weeks. The pregnancies resolved in the third

trimester in 88% (59/67) of women; of these pregnancies, 85% (51/59) of infants were delivered through Cesarean section. Ten of 67 cases (14%) were resolved in the second trimester, with vaginal birth in 100% of them. The main indication for birth in the second trimester was fetal demise.

DISCUSSION

Currently, over 200 skeletal dysplasias have been classified according to phenotype, and a total of 400 cases of skeletal dysplasia have been characterized through their genotype and/or proteins and are reflected in the Nosology and Classification of Genetic Skeletal Disorders (2007). Skeletal dysplasias are the second most common fetal structural disease in prenatal diagnostic centers. The diagnosis of skeletal dysplasia requires additional studies to clarify its origin; guide parents regarding its monitoring, treatment, prognosis and postnatal care; and implement a multidisciplinary management by a group of experts, including a fetal physician, a geneticist, an obstetrician, an anesthesiologist, a neonatologist and an orthopedist, to offer patients a comprehensive approach to improve conditions in pre- and postnatal stages.

Genetic counseling is a communication process that relies on clinical history, family history, laboratory and imaging studies and specialized genetic studies (cytogenetic, enzymatic and molecular) that aims to define the etiology of the disorder, establish prognosis and determine the recurrence risk. For families who previously had a fetus with a confirmed skeletal dysplasia and are at risk of recurrence, the molecular analysis of DNA from chorionic villus sampling (CVS) between 11 and 13 weeks⁹ or amnio-



Figure 3. Cranial depression.



Figure 4. A. Skeletal dysplasia with restrictive chest (prenatal). B. Skeletal dysplasia with restrictive chest (postnatal).

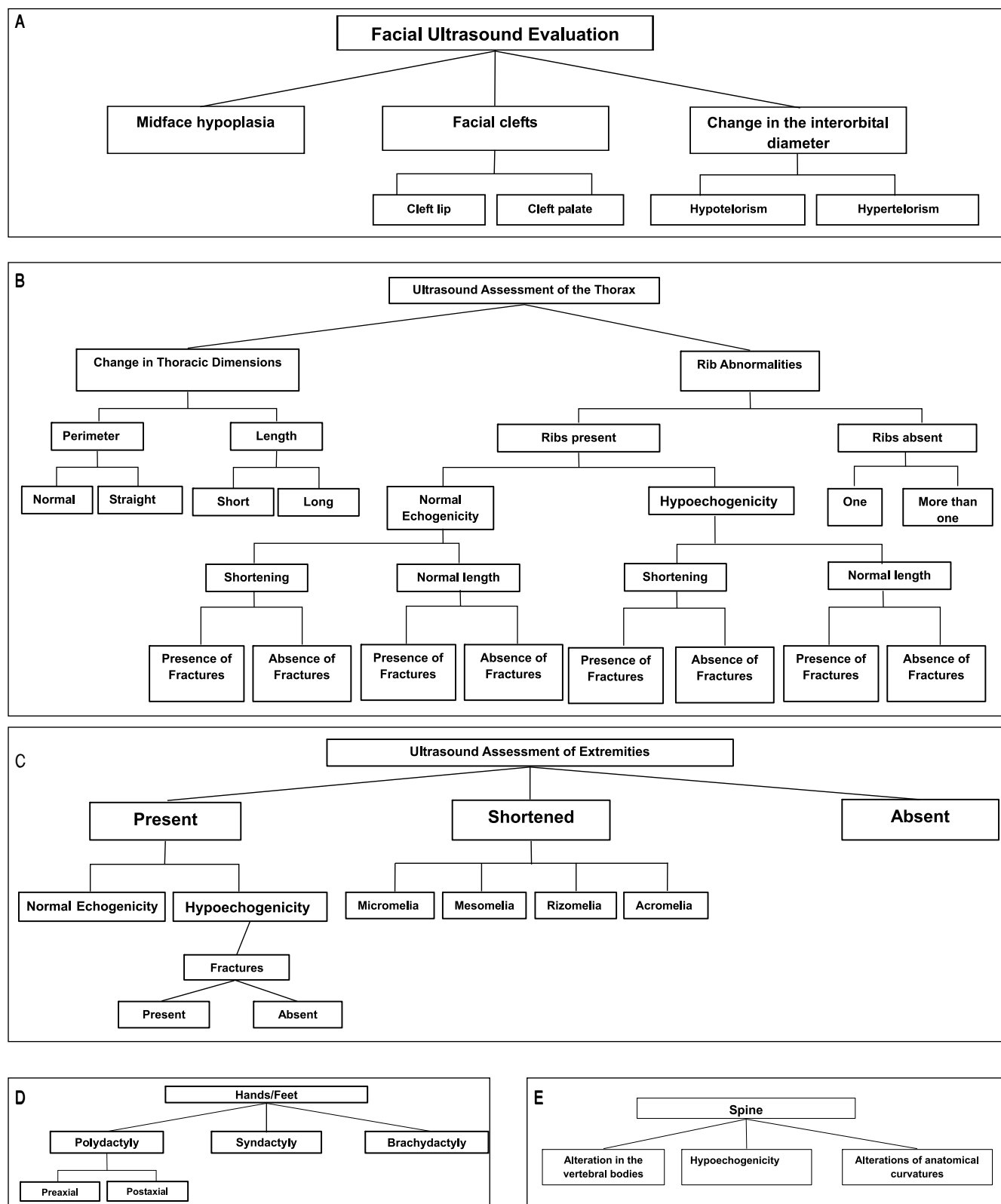


Figure 5. Flowcharts of the diagnostic approach for evaluating dysplasias. A. Facial bone dysplasias. B. Thoracic bone dysplasias. C. Extremity bone dysplasias. D. Bone dysplasias in the hands and feet. E. Spinal bone dysplasias.

centesis between 16 to 20 weeks of gestation is an available option to directly look for mutations.

In Mexico, Ávila, *et al.*, at the La Raza National Medical Center, has retrospectively reviewed reported birth defects from 1984 to 2003, totaling 14,986 newborns with a total of 3,682 malformations (2.46%). The average number of births per year was 7,494, with 184 infants presenting defects each year; congenital abnormalities that affected the musculoskeletal system (19.3% of infants) were second in prevalence only to cardiovascular system defects 26% of the infants.¹⁰ The overall frequency of skeletal dysplasia in perinatal deaths is 9.1/1,000 births.

Despite the increased of validated methods for diagnosing skeletal dysplasia including histological, radiological, ultrasound and molecular techniques, around 7% of cases do not corroborate the diagnosis.¹¹

In our review, the prevalence of skeletal dysplasia is high (8.1 per 10,000 newborns per year *vs.* 2.4 per 10,000 births reported in international literature),^{4,5} which is primarily due the fact that the INPerIER is a national referral hospital for tertiary care, and many high-risk pregnancies in which the fetus has skeletal dysplasia are resolved here. Thus, these results do not reflect the current status of these disorders in our country.

In this review, the four most frequently diagnosed dysplasias were OI (20.8%), followed by achondroplasia (13.4%), thanatophoric dysplasia (13.4%), and short rib polydactyl syndrome (4.4%). This finding coincides with that shown in previous series conducted by Gonçalves and Jeanty in 1993 and Schramm in 2009.^{12,13} In the 67 cases studied, there were 20 different types of dysplasia. Maternal age was not a risk factor for the development of fetal skeletal dysplasia, as previously shown. Most women were between 25 and 29 years of age. These women's infants were most commonly diagnosed during the third trimester, which was a result of late referral by the primary care level, both for confirmation or exclusion of a diagnosis and resolution. Ultrasonographic markers of skeletal dysplasia that were more frequently found in the study were femurs with pronounced curvature ($n = 40$, 59.7%), followed by a decrease in bone density and abnormal cardiothoracic ratio ($n = 21$ each, 31.3%), the prevalence of these markers for diagnosis of skeletal dysplasia is similar to that reported by Romero in 1990.¹⁴ In 29.8% (20/67) of infants, there was shortening of tubular bones, and 14 (20.8%) patients presented with frontal bossing. By analyzing the type of ultrasonographic markers, it is clear that a

thorough review that is sensitized to these changes will be enough for suspected or confirmed cases and will classify the fetal skeletal alteration (Figure 3). We found a total mortality rate of 26.08% (11/67), of which there were a total of 7 deaths and 11 early neonatal deaths. Thanatophoric dysplasia was responsible for 54.5% of deaths in this study (6/11). Within the data reported in this review, only 5.8% of cases had a family history of skeletal dysplasia or other structural defects, which leads to two conclusions: *de novo* mutations account for the presence of disease without a corresponding family history (excluding the cases of skeletal dysplasia with autosomal recessive inheritance), and these defects must be analyzed in the whole population and not only patients who have a family history of the disease.

As showing the results, two complementary evaluations for confirming the diagnoses were often performed incompletely: the karyotype was determined in only 11% of cases, there were no molecular genetic analysis in any of the cases by the lack of availability at the Institute and pathological analysis after fetal or neonatal death was performed in less than half of the cases due the lack of acceptance of the parents. Many of the records had incomplete postnatal outcomes. Similarly, postnatal support was infrequently given to patients. Thus, it necessary to work cooperatively, especially between the medical and paramedical groups, which will subsequently impact the couple and their family and provide continuity to the monitoring of all cases of fetal skeletal dysplasia. We must therefore adhere to diagnosis and management flow charts that are designed to standardize the diagnosis, monitoring, assessment and resolution of cases of fetal skeletal dysplasia. The proposed schemes used in the Fetal Medicine Department of our institution are one option to resolve the issues that we have raised and standardize screening and confirmation/exclusion criteria of the disease (Figure 5).

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