U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2018/2019

Miguel Pereira da Cunha Coelho de Macedo

Prenatal diagnosis of fetal skeletal dysplasias

current state and future perspectives

June, 2020

Miguel Pereira da Cunha Coelho de Macedo

Prenatal diagnosis of fetal skeletal dysplasias

Current state and future perspectives

Mestrado Integrado em Medicina

Área: Ciências Medicas e da Saúde

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutora Carla Ramalho

E sob a Coorientação de:

Doutora Filipa Carvalho

Trabalho organizado de acordo com as normas da revista:

Fetal and Pediatric Pathology

Radiologia Brasileira

Junhe, 2020

U.PORTO

FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Aos meus pais
Para todos os futuros pais

To my parents
For all future parents

FMUP

U.PORTO
FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

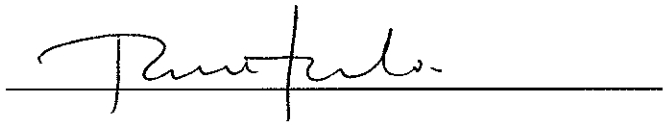
UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

Eu, **Miguel Pereira da Cunha Coelho de Macedo** abaixo assinado, nº mecanográfico **201405925** estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 30/3/2020

Assinatura conforme cartão de identificação:



U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

Miguel Pereira da Cunha Coelho de Macedo

NÚMERO DE ESTUDANTE	E-MAIL
201405925	miguel_macedo2@hotmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências médicas e da saúde – medicina clínica

TÍTULO DISSERTAÇÃO

Fetal Skeletal Dysplasias: Current and future perspectives

ORIENTADOR

Professora Doutora Carla Ramalho

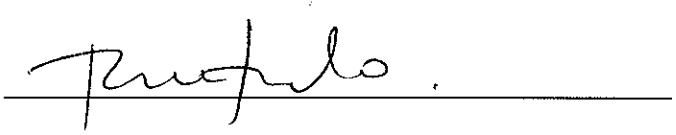
COORIENTADOR

Professora Doutora Filipa Carvalho

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 31/3/2020

Assinatura conforme cartão de identificação: 

Artigos / Articles

(1) **Pereira-Macedo M**, Carvalho F, Guimaraes S, Rebelo S, Ramalho A. Early Gestational Diagnosis of Lethal Skeletal Dysplasias : A 15 year retrospective cohort reviewing concordance between ultrasonographic, genetic and morphological features Fetal Pediatr Pathol 2020 doi 10.1080/15513815,2020,1761915

(2) **Pereira-Macedo M,** Werner H, Araujo-Junior Fetal Skeletal Dysplasias: a new way to look at them Radiol Bras 2020 Mar/Abr;53(2):112-113 doi:10,1590/0100-3984,2018,0140

FETAL AND PEDIATRIC PATHOLOGY
https://doi.org/10.1080/15513815.2020.1761915

Taylor & Francis
Taylor & Francis Group

Early Gestational Diagnosis of Lethal Skeletal Dysplasias: A 15 Year Retrospective Cohort Reviewing Concordance between Ultrasonographic, Genetic and Morphological Features

Miguel Pereira Macedo[a,b], Filipa Carvalho[b,c], Susana Guimarães[d], Sandra Rebelo[b,e], and Carla Ramalho[a,b]

[a]Department of Obstetrics, Gynecology and Pediatrics Faculty of Medicine University of Porto, Portugal; [b]University of Porto, Instituto de Investigação e Inovação em Saúde Porto Portugal; [c]Department of Genetics Centro Hospitalar Universitário São João Porto Portugal; [d]Department of Pathology Centro Hospitalar Universitário São João Porto Portugal; [e]Department of Experimental Biology Faculty of Medicine University of Porto, Porto Portugal

ABSTRACT

Aim: We evaluated the diagnostic accuracy of ultrasound, postmortem and genetic studies in classifying skeletal dysplasias in the first vs second trimester of pregnancy.

Methods: We retrospectively gathered data from a 15 year period of all the prenatal ultrasounds, autopsies, and available genetic studies on fetuses with skeletal dysplasias from our institution.

Results: Five (23%) and 17 (77%) fetuses were diagnosed during the first and second trimester of pregnancy respectively. Only partial characterization was possible with ultrasound in the first trimester. Complete characterization was established in five cases (30%) in the second trimester with ultrasound alone. Pathology provided an additional diagnostic yield of 40% and 47% and genetics an additional 40% and 11% in the first and second trimesters respectively.

Conclusion: Ultrasound is an effective screening but not a diagnostic tool. Complete characterizations of dysplasia increased from 22% by ultrasound alone to 86% with pathology and genetics.

ARTICLE HISTORY
Received 27 January 2020
Revised 2 April 2020
Accepted 7 April 2020

KEYWORDS
fetal skeletal dysplasias; ultrasound; Monogenic diseases; Pathology; Diagnosis

Introduction

Skeletal dysplasias are a heterogeneous group of more than 350 diseases of genetic etiology affecting bone and cartilage. They show diversity in their form of inheritance, natural history, treatment and prognosis. The great degree of phenotypic variation makes diagnosis based on ultrasound alone particularly challenging. Although substantial progress in the identification of the underlying genetic defect has been achieved in recent years and has become a valuable complement to sonographic evaluation, it is not routinely practiced [1].

With an estimated prevalence of 2/10 000 births, these are uncommon fetal malformations [2]. About 50% of these are compatible with life. Of the remaining cases 23%

CONTACT Miguel Pereira Macedo miguel_macedo2@hotmail.com Department of Obstetrics Gynecology and Pediatrics , Al. Prof. Hernâni Monteiro, University of Porto Faculty of Medicine, Porto 4200-319, Portugal.

are stillborn and 32% die during the first week of life [3]. An early distinction between lethal and non-lethal forms is therefore of great importance as it allows timely counseling of parents regarding fetal outcomes as well as risk calculation for future gestations.

This article reviews first and second trimester ultrasound, pathology and genetic reports that suggest or confirm the diagnosis of skeletal dysplasia and its subtype. The diagnostic contributions of each exam modality are assessed and concordance between outcomes compared.

Materials and methods

A retrospective study was performed in a tertiary university hospital. All cases of skeletal dysplasia, irrespective of type, submitted for termination of pregnancy (TOP) from 2002 to 2018 from a mixed referral and screening population were included. Data was collected from electronic clinical databases regarding ultrasound, genetic and pathological evaluations. Cases are chronologically ordered.

The first trimester ultrasound examination included crown-rump length (CRL), nuchal translucency (NT), ductus venosus (DV) and nasal bone (NB) evaluation. CRL was used to calculate gestational age in all cases. The second trimester ultrasound examination included measurement of the long bones in all segments of all four extremities, examination of the hands, spine and head and assessment of mineralization and bone shapes, in addition to a full fetal anatomical survey [4]. For the purposes of this study, biometric data (femur length (FL), biparietal diameter (BPD), head circumference (HC) and thoracic circumference (ThC)) were collected and analyzed in relation to published normal values [5]. Karyotype was available in all cases. Additional genetic studies, including array comparative genomic hybridization (aCGH) and molecular studies (targeted gene, skeletal dysplasia panel or multi gene panel) were undertaken after ultrasound evaluation or after evaluation of necropsy study.

Termination of pregnancy was performed according to a pharmacological protocol with mifepristone and misoprostol. After 22 weeks of gestation, feticide was systematically adopted.

Parental informed consent was always obtained before autopsy. All cases were submitted to postmortem examination at the Developmental Perinatal Unit of the Department of Pathology, according to standardized procedures previously described [6]. Macroscopic, radiological and histological study were performed in all cases.

A correlation between ultrasound and pathology was performed. “Complete” corresponds to complete concordance between ultrasound and pathology. “Partial” refers to cases where the postmortem dysplasia was more specific than the ultrasound diagnosis. When available, genetic studies were undertaken to validate diagnosis. “Undefined skeletal dysplasia” refers to cases where dysplasia is seen on ultrasound but the subtype was not fully characterized by ultrasound, pathology and/or genetics.

The study was approved by the S. João University Hospital Ethics Committee.

Statistical analysis was performed with SPSS Statistics. Continuous variables were analyzed and expressed by the median due to their non-normal distribution. Percentages illustrate the number of cases diagnosed at each step.

Results

In this study we included 22 fetuses from TOP in which skeletal dysplasia was diagnosed by prenatal ultrasound. This represented 22/671 (3.3%) of all TOP due to fetal pathology. Median maternal age at diagnosis was 32 (range 26-42) years, median gestational age at ultrasound diagnosis 18 weeks (range 11-22) and median age at autopsy 22 weeks (range 12-28). Male fetuses represented 59% of cases and female 41%.

First trimester

Five fetuses (23%) were diagnosed with some form of skeletal dysplasia during the first trimester of pregnancy (Table 1, Figures 1 and 2). For this subgroup median maternal age at diagnosis was 34 years (range 29-40), the median gestational age at ultrasound diagnosis was 12 weeks (range 11-13). The median gestational age of pathology examination was 14 weeks (range 12-15). The median gestational age of pathology was 14 weeks range (12-15). Three fetuses were male and two were female. One case was from a bichorionic biamniotic twin pregnancy (case 16) (Table 1). In this particular case, post mortem analysis was not completed due to poor specimen preservation. Complete skeletal dysplasia characterization was achieved in 4/5 (80%) of cases and partially characterization in 1/5 (20%)

Ultrasound

Only partial characterization was possible with ultrasound during the first trimester scan. No incorrect ultrasound diagnosis was described. No specific skeletal dysplasia subtype was identified based on imaging alone. Limb morphology regarding long bones was the most frequent morphological alteration .

Genetics

Karyotype analysis showed no chromosomal alterations in any of the five cases. The twin pregnancy was characterized by a normal 46,XY fetus and an abnormal 46,XX fetus with p.Gly974Cys in COL1A1gene (case 16). Case 19 was diagnosed with Grieg Syndrome with p.Gln1103□ inGLI3gene. When performed, genetics alone contributed to the complete characterization of dysplasia subtype in 1/5 (20%) of first trimester cases.

Pathology

Pathology alone provided complete characterization in 2/5 (40%) cases. In no case was the diagnosis of skeletal dysplasia ruled out by pathological findings. Addition information was gained mainly with regards to bone structure and cardiac morphology.

Second trimester

Seventeen fetuses (77%) were diagnosed with some form of skeletal dysplasia during the second trimester of pregnancy (Table 2). For this subgroup median maternal age at

Table 1. Cases diagnosed in the first trimester scan: Main morphological ultrasound findings, nuchal translucency, additional pathology autopsy information, genetic studies and final diagnosis.

Case number	Gestational age a US (weeks)	Ultrasound findings	Nuchal translucency	Gestational age at pathology examination (weeks)	Pathology finding	Genetics	Final diagnosis	Concordance between US and pathology
1	12	Hydropsia Micromelia Narrow thorax	Abnormal	13	Disorganized and undifferentiated epiphysial chondrocytes, tricuspid valve dysplasia	NP	Achondrogenesis type 1B	Partial
9	11	Short lower limbs	Abnormal	12	Disorganized endochondral bone structure more exuberant in the hypertrophic area	NP	Thanatophoric dysplasia	Partial
16	12	Short upper limbs Hypoplastic forearm bones Abnormal right hand posture	Abnormal	15	NP	p.Gly974Cys in COL1A1 gene (skeletal dysplasia panel)	Osteogenesis imperfecta	Partial
19	12	Shortened bones Increased subarachnoid space cardiopathy	Abnormal	15	Complete atrioventricular septal defect.	p.Gln1103□ in GLI3 gene (multi gene panel)	Greig Syndrome	Partial□
21	13	Severe tibial and fibula hypoplasia Ectrodactyly right foot	Normal	14	Three Supernumerary medial fingers with slight cutaneous syndactyly	Normal aCGH	USD	USD

NP – not performed.
USD – undefined skeletal dysplasia.
□Final diagnosis by genetic studies.

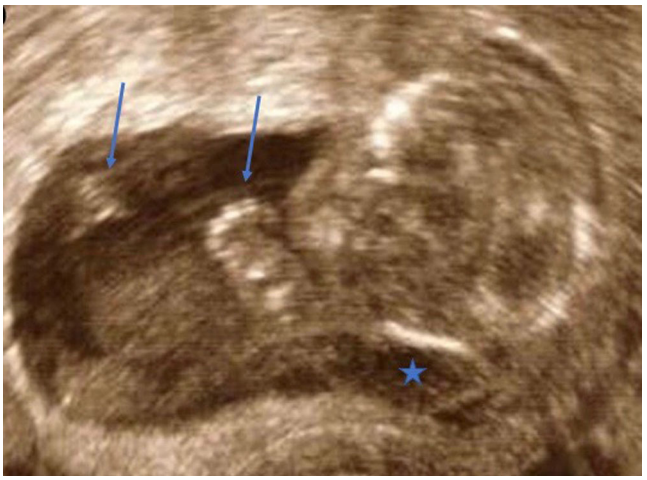


Figure 1. Ultrasound of Case 1. Achondrogenesis type 1B at 12 weeks: micromelia (arrows), narrow thorax, subcutaneous edema (star).

diagnosis was 32 years (range 26-42), median gestational age at ultrasound was 21 weeks (range 16-22) and median gestational age at autopsy was 22 weeks (range 17–28). Nine fetuses were male and eight were female. Complete skeletal dysplasia characterization was achieved in 15/17 (88%) of cases. Case 14 and 17 were from the same mother.

Ultrasound

Complete characterization was established in five cases (30%) and partial characterization in 12/17 (70%). In all recorded cases, the first trimester scan had shown nuchal translucency within normal range, normal flow in the ductus venosus and the presence of nasal bones. Long bone morphology of the limbs remained an important diagnostic contributor, but cranial and finger number alternations become relevant sources of information.

Genetics

Karyotyping showed no chromosomal abnormalities in any case. From the 17 cases with genetics studies, these provided the final diagnosis in two (12%) and in six (35%) confirmed pathology findings. aCGH identified two cases with pathological alterations and one case classified as possibly pathogenic because it did not explain the morphological changes observed. In two cases specific pathogenic sequence variations were found by targeted gene studies and in three by skeletal dysplasia panels.

Pathology

In no case was the ultrasound diagnosis of skeletal dysplasia ruled out by pathological findings. Pathology alone provided the complete characterization in 8/17 (47%) of cases.

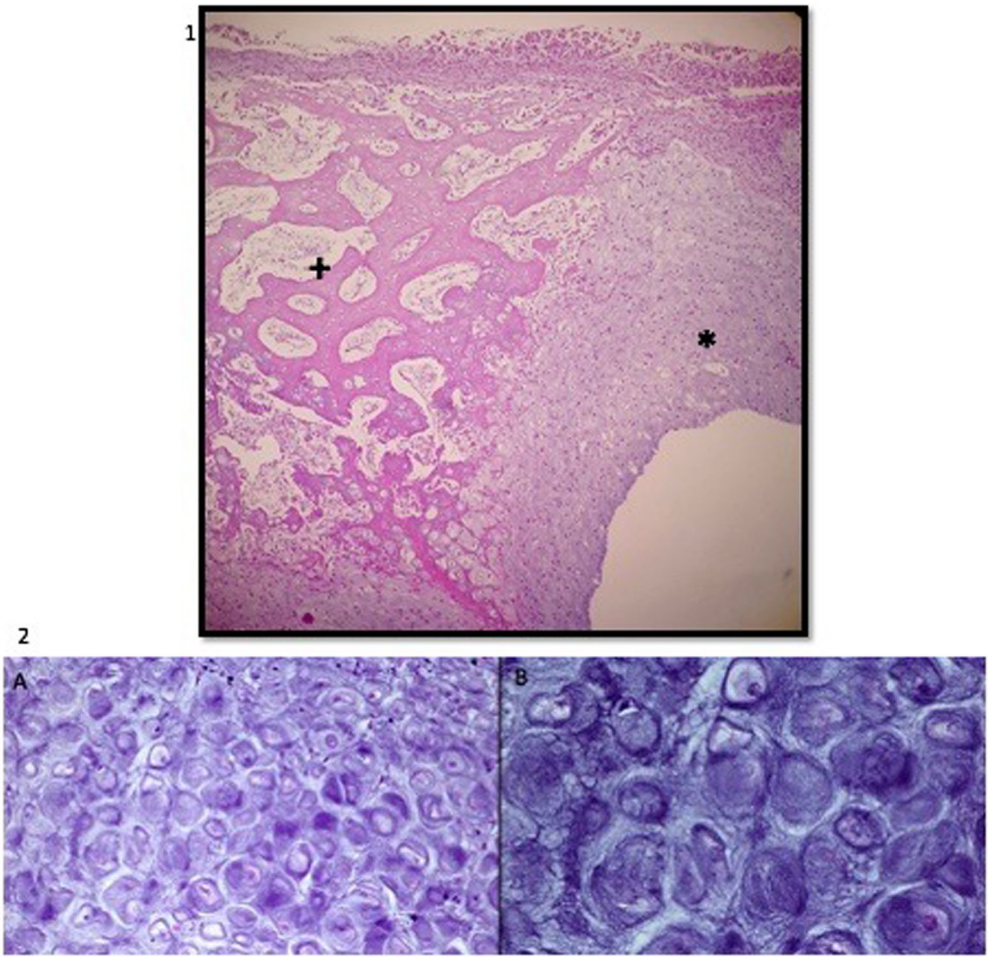


Figure 2. Histological examination of case 1. Achondrogenesis type 1B: 1 (H&E, x20) showing the left femur, with resting cartilage on the right (□) and advanced endochondrial ossification on the left (þ); 2 A (H&E, □200) and 2B (H&E, □400) showing resting cartilage: celular disorganized cartilage, with malformed agreggation of swollen chondrocytes with reduced matrix.

Discussion

In our study, skeletal dysplasias represent a 3.3% of all TOP, a slightly smaller percentage than previous studies [2]. Although detection of a lethal dysplasia was always achieved, correct classification of the dysplasia subtype by ultrasound alone remained challenging. No single first trimester screening parameter practiced clinically exhibited consistent alterations in cases of lethal skeletal dysplasia. Of all, nuchal translucency was the most frequently altered parameter but only in 18% of all cases. Increased NT in the first trimester scan had a high association with dysplasia in line with previous findings [7] but when within normal limits did not prove effective in excluding it. Ultrasound diagnosis remains highly dependent on morphological analysis, especially of limbs, thorax and skull. It was most effective during the second trimester of pregnancy, when skeletal abnormalities can be better perceived [8,9].

Table 2. Cases diagnosed in the 2nd trimester scan: Main morphological ultrasound findings, additional pathology autopsy information, genetic studies and final diagnosis.

Case number	Gestational age at US (weeks)	Ultrasound findings	Gestational age at autopsy (weeks)	Pathology findings	Genetics	Final Diagnosis	Concordance
2	16	Narrow thorax, small ribs Short limbs Polydactyly	22	Irregular rib growth plates, narrowed proliferative and hypertrophic areas with disorganized chondrocyte columns	NP	Asphyxiating thoracic dystrophy	Partial
3	18	Narrow thorax, small ribs	22	Hyperflexion of the hands and clinodactyly of the 2nd finger of left hand and clinodactyly of the 3th and 4th fingers of right hand, rocker-bottom foot Cervicothoracic scoliosis, marked narrowing of the ribcage, short/thin ribs and disorganized phseal growth zones	NP	Short rib polydactyly syndrome Saldino-Noonan subtype	Complete
4	17	Cloverleaf skull Narrow thorax Short ribs Abdominal / thoracic disproportion Rhizomelia	18	Cloverleaf skull with lateral fusion of frontal-parietal bones, wide set eyes and flat mid face. Platyspondyly, short ribs, short straight long bones Costochondral growth plate with poorly formed columns of chondrocytes	NP	Thanatophoric dysplasia type 2	Complete
5	22	Short long bones	23	Bulging forehead, depression of root of nose. Short limbs and rhizomelic disproportion Narrow / disorganized zones of proliferation and hypertrophy in growth plates. Chondrocytes in clusters	p.Gly380Arg in FGFR3 gene (targeted analysis)	Achondroplasia	Partial
6	21	Lemon sign Narrow thorax Short limbs	21	Absent ossification cranial vault, brittle cartilaginous bones with multiple fractures. Short beaded ribs. Small chest and lungs for gestational age	NP	Osteogenesis imperfecta IIC	Partial
7	22		23				Partial

(continued)

Table 2. Continued.

Case number	Gestational age at US (weeks)	Ultrasound findings	Gestational age at autopsy (weeks)	Pathology findings	Genetics	Final Diagnosis	Concordance
		Short long bones Micrognathia Bilateral clubfoot Agenesis of phalanxes		Retromicrognathia, low bilateral ear pavilion implantation. Absent ossification centers of cervical vertebral bodies, 11 rib thin rib pairs, bilateral absence of first metacarpal, fibrosis and cystic EC matrix	No pathogenic variations detected in exon 2 and 3 of SLC26A2 (targeted analysis)	Atelosteogenesis type 2	
8	21	Narrow thorax Rhizo and mesomélic shortening of limbs	21	Asymmetrical growth restriction, absent ossification of cranial vault. Delicate cartilaginous bones with multiple fractures and callus formation. Short deformed limbs and short beaded ribs. Hypoplastic lungs	NP	Osteogenesis imperfecta IIA	Partial
10	22	Abnormal posture Long bones P5	23	Poorly ossified cranial vault. Multiple fractures of long bones with angulation	NP	Osteogenesis imperfecta IIB	Partial
11	18	Narrow thorax Rhizomelic shortening limbs	18	Thoracic and lumbar platyspondyly Bilateral club foot	NP	USD	USD
12	21	Polydactyly	24	Small chin, low set ears with backward rotation of auricles. Post axial polydactyly. Short ribs and lung hypoplasia. Double cardiac inlet and outlet. Atresia of aortic valve. Delayed ossification of physeal growth zones.	Normal aCGH	Ellis van Creveld Syndrome	Partial
13	21	Agenesis right radium Hypoplasia left radium	22	Agenesis right radius Hypoplasia left radium Permanent flexion upper limbs	arr 1q21.1 (15,291,711-145,833,054)x1 (aCGH)	TAR Syndrome	Complete
14	17	Rhizomelic shortening limbs Dandy Walker syndrome	17	Short neck Short thorax Bilateral cubital deviation of fingers Abnormal ilium Irregular endochondral growth	p.Arg1817□/ p.Ser3696□ in HSPG2 gene (skeletal dysplasia panel)	Autossomic recessive Silverman-Handmarker dysplasia	Partial□

15	21	Slight bilateral ventriculomegaly, bilateral sindactly of 2,3,4 fingers. Absent thumbs bilaterally	24	Brachycephaly, proptosis, hypertelorism, short nose, low ear pavilion insertion, bilateral synostosis of coronal cranial sutures. Symmetric bilateral syndactyly of upper and lower limbs	p.Pro253Arg in FGFR2 gene (skeletal dysplasia panel)	Apert Syndrome	Complete
17	21	Narrow thorax Rhizomelic shortening limbs	28	Short neck Short thorax Bilateral cubital deviation of fingers Abnormal ilium Irregular endochondral growth	p.Arg1817□/ p.Ser3696□ in HSPG2 gene (skeletal dysplasia panel)	Autossomic recessive Silverman-Handmarker dysplasia	Partial □
18	16	Short femurs with bilateral fractures . Right club foot	17	Low ear pavilion insertion, short large neck, short thorax, four segment micromelia, bilateral cubital deviation of fingers. Internal rotation of feet. Vertebral bodies with decreased and dispersed ossification centers. irregular organization of hypertrophic zone.	p.Lys145Argfs□47 in PPIB gene (targeted analysis)	Osteogenesis imperfecta IIA	Complete
20	21	Short lower limb and feet	22	Agenesis of right fibula, angulated right tibia, osteosclerosis right foot only three toes	NP	FATCO syndrome	Partial
22	22	Mesomelic shortening of lower limb	22	Fibular aplasia Tibial campomelia oligosyndactyly	arr Xp21.2 (31,139,936-31,375,215)x3 (aCGH)	USD	USD

NP – not performed.
USD – undefined skeletal dysplasia.
□Final diagnosis by genetic studies.

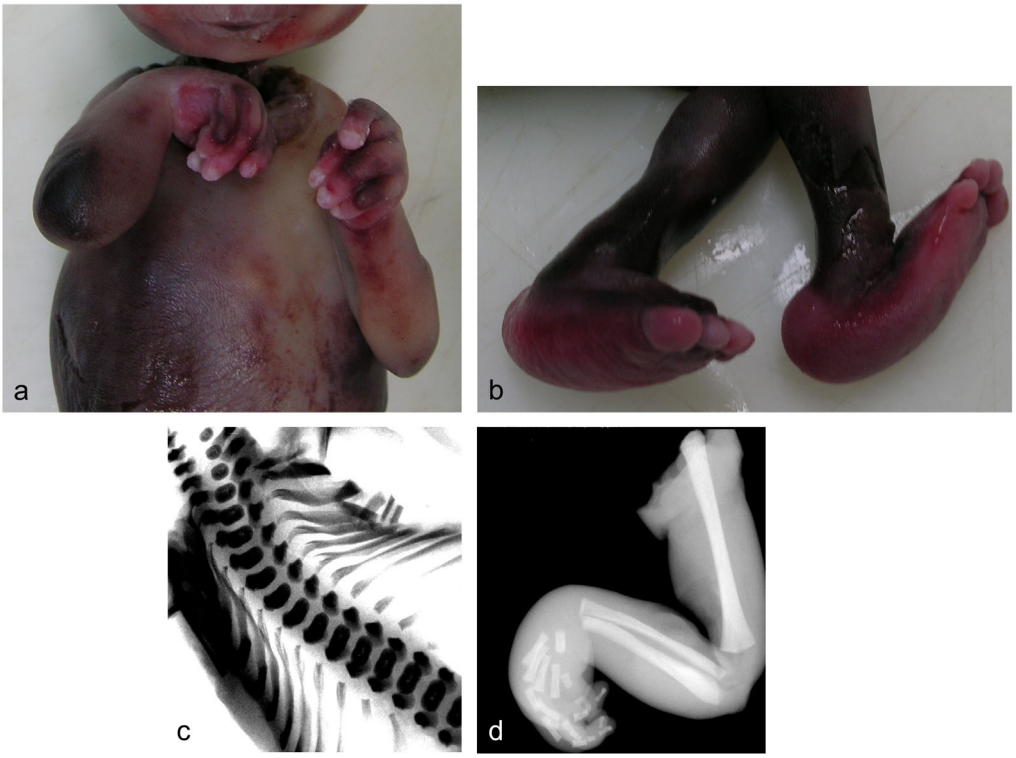


Figure 3. Pathology examination of case 3. Short rib polydactyly syndrome: macroscopy (a, b): hyperflexion of the hands and clinodactyly of the 2nd finger of left hand and clinodactyly of the 3th and 4th fingers of right hand (a); rocker-bottom feet (b). Radiological examination (c, d) Cervicothoracic scoliosis, marked narrowing of the ribcage, short/thin ribs, almost parallel (c); long bone growth discrepancy: normal ulna P50, short radius P5 and short humerus P10 (d).

Although a greater number of cases were identified in the first trimester, when compared with older studies [10] chronological analysis of diagnosis success does not show a higher percentage of complete characterizations in recent years. It can be inferred that despite better ultrasound equipment with increased image quality, diagnostic accuracy has not increased with time. In our series only 30% of second trimester cases were completely characterized by ultrasound alone, percentages similar to those achieved 20 years ago [11]. Even with further technological advances, more specific and earlier diagnosis is unlikely. Other diagnostic methods should therefore be considered to increase diagnostic yield [12,13].

The postmortem pathology examination represents an important adjuvant to specific dysplasia subtype characterization (Figure 3). In our series, it alone provided 40% and 47% of complete dysplasia characterizations in the first and second trimesters respectively. Osteogenesis imperfecta was the most frequent final diagnosis (22%) in line with previous literature [14]. Results reinforce the use and need for systematic evaluation of all cases of TOP by autopsy as previously stated for other conditions [15,16]. These highlight the importance of corroboration or adjustment of the final diagnoses, quality control of the sonographic assessment as well as future parental counseling.

Karyotyping showed no chromosomal abnormalities in any case. More specific genetic studies including a-CGH, skeletal dysplasia panels and targeted gene analysis all

contributed to specific diagnosis. When undertaken, genetic studies were fundamental in the characterization of one case (20%) in the first trimester and two cases (12%) in the second trimester. In the remaining cases they confirmed pathology diagnosis. Their regular application could be used in the first trimester when dysplasia is suggested by ultrasound. However, the use of skeletal dysplasia panels as a screening method alone would presently not be a substitute for ultrasound, in agreement with Zhou et al (2018) due to the low frequency of these diseases [17]. Next generation sequencing shows great promise in improving prenatal diagnosis of skeletal dysplasia [18]. When couples decide for TOP, we suggest that genetic studies should follow pathology examination as pathology and ultrasound together were able to fully characterize 72% of dysplasias.

In our study the addition of pathology and genetics to ultrasound alone increased complete dysplasia characterizations from 22% to 86%. Ultrasound can therefore be viewed as an effective screening tool for the presence of dysplasia but not for its classification. Future diagnostic approaches should incorporate new diagnostic imaging approaches as well as pathology and genetics. One limitation to our study is the relatively small number of cases. However, due to the frequency of these conditions and concordance with previous studies we believe its conclusions are an important addition to the limited literature available.

Disclosure statement

The authors declare no conflict of interest.

ORCID

Miguel Pereira Macedo http://orcid.org/0000-0002-7828-8900
Filipa Carvalho http://orcid.org/0000-0001-9546-4614
Sandra Rebelo http://orcid.org/0000-0002-5358-5204
Carla Ramalho http://orcid.org/0000-0002-3977-3946

References

[1] Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, Mundlos S, Nishimura G, Rimoin DL, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet. 2011;155(5):943–68. doi:10.1002/ajmg.a.33909.

[2] Barkova E, Mohan U, Chitayat D, Keating S, Toi A, Frank J, Frank R, Tomlinson G, Glanc P. Fetal skeletal dysplasias in a tertiary care center: radiology, pathology, and molecular analysis of 112 cases. Clin Genet. 2015; Apr87(4):330–7. doi:10.1111/cge.12434.

[3] Camera G, Mastroiacovo P. Birth prevalence of skeletal dysplasias in the Italian multicentric monitoring system for birth defects. Prog Clin Biol Res. 1982; 104:441–9.

[4] Meizner I. Fetal skeletal malformations revisited: steps in the diagnostic approach. Ultrasound Obstet Gynecol. 1997;10(5):303–206. doi:10.1046/j.1469-0705.1997.10050303.x.

[5] Snijders RJM, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. Ultrasound Obstet Gynecol. 1994;4(1):34–48. doi:10.1046/j.1469-0705.1994.04010034.x.

[6] Ramalho C, Brandão O, Monterroso J, Matias A, Montenegro N. Cardiac findings in routine fetal autopsies: more than meets the eye?. Eur J Obstet Gynecol Reprod Biol. 2012; 163(2):142–7. doi:10.1016/j.ejogrb.2012.04.019.

[7] Ngo C, Viot G, Aubry MC, Tsatsaris V, Grange G, Cabrol D, Pannier E. First-trimester ultrasound diagnosis of skeletal dysplasia associated with increased nuchal translucency thickness. Ultrasound Obstet Gynecol. 2007;30(2):221–6. doi:10.1002/uog.4028.

[8] Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. Prenat Diagn. 2011;31(1):90–102. doi:10.1002/pd.2642.

[9] Syngelaki A, Hammami A, Bower S, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11–13 weeks' gestation. Ultrasound Obstet Gynecol. 2019;54(4):468–76. doi:10.1002/uog.20844.

[10] Doray B, Favre R, Viville B, Langer B, Dreyfus M, Stoll C. Prental sonographic diagnosis of skeletal dysplasias. A report of 47 cases. Ann Genét. 2000; 43(3-4):163–9. doi:10.1016/S0003-3995(00)01026-1.

[11] Gaffney G, Manning N, Boyd PA, Rai V, Gould S, Chamberlain P. Prenatal sonographic diagnosis of skeletal dysplasias – a report of the diagnostic and prognostic accuracy in 35 cases. Prenat Diagn. 1998; 18(4):357–62. doi:10.1002/(SICI)1097-0223(199804)18:4<357::AID-PD276>3.0.CO;2-0.

[12] Cassart M, Massez A, Cos T, Tecco L, Thomas D, Van Regemorter N, Avni F. Contribution of three-dimensional computer tomography in the assesment of fetal skeletal dysplasia. Ultrasound Obstet Gynecol. 2007; 29(5):537–43. doi:10.1002/uog.4001.

[13] Santos XM, Papanna R, Johnson A, Cass DL, Olutoye OO, Moise KJ, Belleza-Bascon B, Cassady CI. The use of combined ultrasound and magnetic resonance imaging in the detection of fetal anomalies. Prenat Diagn. 2010; 30(5):402–7. doi:10.1002/pd.2481.

[14] Schramm T, Gloning KP, Minderer S, Daumer-Haas C, Hörtnagel K, Nerlich A, Tutschek B. Prenatal sonographic diagnosis of skeletal dysplasias. Ultrasound Obstet Gynecol. 2009; 34(2):160–70. doi:10.1002/uog.6359.

[15] Ramalho C, Matias A, Brandão O, Montenegro N. Critical evaluation of elective termination of pregnancy in a tertiary fetal medicine center during 43 months: correlation of prenatal diagnosis findings and postmortem examination. Prenat Diagn. 2006;26(11): 1084–8. doi:10.1002/pd.1567.

[16] Ramalho C, Brandão O, Matias A, Montenegro N. Systematic fetal autopsy in cases of medical termination of pregnancy due to chromosomal abnormalities: improving the quality of perinatal care?. Prenat Diagn. 2010;30(10):1000–4. doi:10.1002/pd.2605.

[17] Zhou X, Chandler N, Deng L, Zhou J, Yuan M, Sun L. Prenatal diagnosis of skeletal dysplasias using a targeted skeletal gene panel. Prenat Diagn. 2018;38(9):692–9. doi:10.1002/pd.5298.

[18] Liu Y, Wang L, Yang Y-K, Liang Y, Zhang T-J, Liang N, Yang L-M, Li S-J, Shan D, Wu Q-Q. Prenatal diagnosis of fetal skeletal dysplasia using targeted next-generation sequencing:an analysis of 30 cases. Diagn Pathol. 2019; 1314(1):76. doi:10.1186/s13000-019-0853-x.

http://dx.doi.org/10.1590/0100-3984.2018.0140

Fetal skeletal dysplasias: a new way to look at them

Displasias esqueléticas fetais: uma nova maneira de olhar

Miguel Pereira Macedo[1,a], Heron Werner[2,b], Edward Araujo Júnior[3,4,c]

1. Unit of Experimental Biology – Department of Biomedicine Center for Medical Research, Faculty of Medicine, University of Porto, Porto, Portugal. 2. Department of Radiology, Clínica de Diagnóstico Por Imagem (CDPI), Rio de Janeiro, RJ, Brazil. 3. Department of Obstetrics, Escola Paulista de Medicina da Universidade Federal de São Paulo (EPM-Unifesp), São Paulo, SP, Brazil. 4. Medical Course, Universidade Municipal de São Caetano do Sul (USCS), Campus Bela Vista, São Paulo, SP, Brazil.

Correspondence: Dr. Edward Araujo Júnior. Rua Belchior de Azevedo, 156, ap. 111, Torre Vitória, Vila Leopoldina. São Paulo, SP, Brazil, 05089-030. Email: araujojred@terra.com.br.

a. https://orcid.org/0000-0002-7828-8900; b. https://orcid.org/0000-0002-8620-7293; c. https://orcid.org/0000-0002-6145-2532.

Received 6 December 2018. Accepted after revision 22 January 2019.

How to cite this article:

Macedo MP, Werner H, Araujo Júnior E. Fetal skeletal dysplasias: a new way to look at them. Radiol Bras. 2020.

Skeletal dysplasias are a heterogeneous group of over 450 genetic diseases affecting bone and cartilage. They have an incidence of 2/10,000 live births and a lethality of approximately 50%, which makes their prenatal diagnosis of particular importance in determining fetal outcomes as well as in genetic counseling for future pregnancies[1].

Ultrasound has for many years been the preferred method of screening for these conditions. Despite significant advances in the last decades regarding image quality and acuity, the diagnostic success rate remains disappointingly low, a correct ultrasound diagnosis being made in only 67.9% of cases[2]. Therefore, new diagnostic modalities should be considered to maximize morphological information. Magnetic resonance imaging (MRI) and computed tomography (CT) have both proven to be useful adjuncts in these conditions. Both techniques have the advantage of being operator independent and not being limited by maternal body mass index or the presence of oligohydramnios. Because it allows three-dimensional (3D) reconstruction, CT has proven to be a valuable complement in selected cases of fetal skeletal dysplasia in which the specific diagnosis cannot be made by ultrasound alone. It has been shown to be superior to ultrasound for the evaluation of bone abnormalities, especially those involving the skull, ribs, or pelvic bones[3]. The diagnostic gain comes from an appreciation of the morphology and deformities in their entirety. Although the use of CT is controversial because it exposes patients to radiation, it has not been shown to increase the occurrence of malformations; if used judiciously, its benefits may well outnumber its risks[4]. Regarding safety, unenhanced MRI (i.e., that performed without contrast) has not been associated with teratogenic or adverse fetal effects. However, its use is currently not recommended before 22 weeks of gestation, and, even thereafter, it should be performed in 1.5 T scanners. The initial MRI evaluation of congenital anomalies should include T1- and T2-weighted sequences. If musculoskeletal disorders are suspected, echo-planar imaging, thick-slab T2-weighted sequences, dynamic steady-state free precession sequences, and volumetric interpolated breath-hold examination sequences should be performed[5]. T2-weighted MRI appears particularly useful in the study of the fetal brain, as well as in that of organs with high water content, which should be evaluated with a T2-weighted half-Fourier single-shot turbo spin echo protocol[6]. For limb deformities, clubfoot, and arthrogryposis, 3D images obtained through thick-slab T2-weighted sequences generate easily recognizable images of the deformities with the additional advantage of the shine-through effect. Data collected with these techniques allow 3D reconstructions to be modeled into virtual reality constructs or 3D-printed representations (Figures 1 and 2), both of which are useful tools for fetal surgeons who are preparing to perform *in utero* or early postnatal corrective surgery[7]. Such imaging techniques can also give parents a greater, more tangible understanding of the defect, as well as strengthening the maternal-fetal attachment[8].

Figure 1. Thoraco-omphalopagus conjoined twins at 31 weeks of gestation. **A:** 3D view from a CT scan. **B:** 3D-printed model.

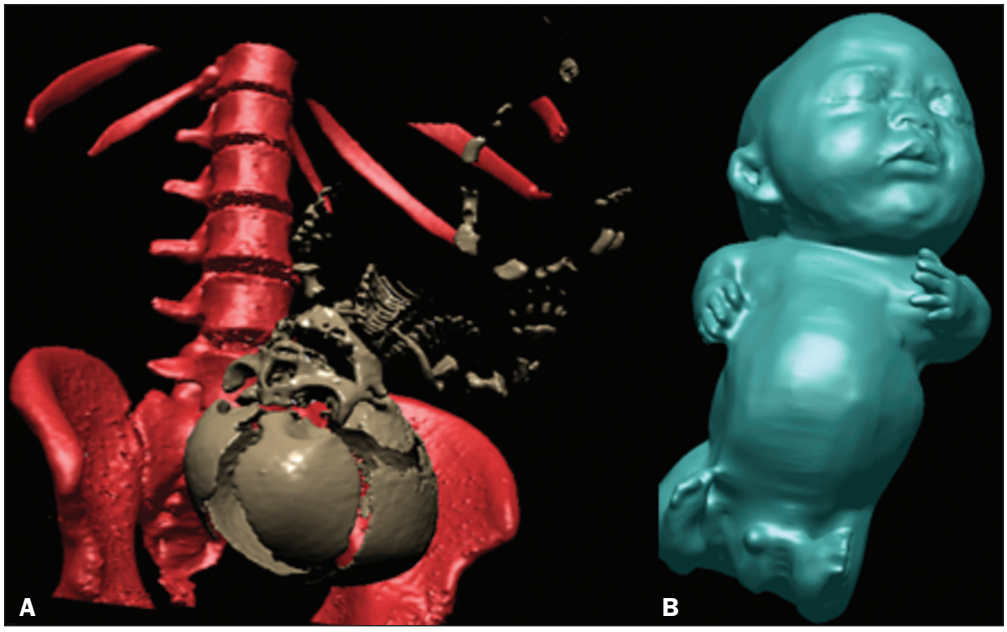


Figure 2. Achondrogenesis at 34 weeks of gestation. **A:** 3D view from a CT scan. **B:** 3D view from an MRI scan.

Ultrasound continues to be an invaluable tool in the screening and diagnosis of fetal skeletal dysplasias and will not be replaced by either CT or MRI used in isolation. Rather, these serve as complementary imaging techniques that increase the overall sensitivity and specificity of the analysis, allowing a greater number of correct and early prenatal diagnoses.

REFERENCES

1. Warman ML, Cormier-Daire V, Hall C, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;155A:943–68.
2. Schramm T, Gloning KP, Minderer S, et al. Prenatal sonographic diagnosis of skeletal dysplasias. Ultrasound Obstet Gynecol. 2009; 34:160–70.
3. Ulla M, Aiello H, Cobos MP, et al. Prenatal diagnosis of skeletal dysplasias: contribution of three-dimensional computed tomography. Fetal Diagn Ther. 2011;29:238–47.
4. Cassart M, Massez A, Cos T, et al. Contribution of three-dimensional computed tomography in the assessment of fetal skeletal dysplasia. Ultrasound Obstet Gynecol. 2007;29:537–43.
5. Nogueira RA, Werner H, Daltro P, et al The role of a novel magnetic resonance imaging sequence in the evaluation of the fetal skeleton: a pilot study. Radiol Bras. 2018;51:303–7.
6. Gonçalves LF, Lee W, Mody S, et al Diagnostic accuracy of ultrasonography and magnetic resonance imaging for the detection of fetal anomalies: a blinded case-control study. Ultrasound Obstet Gynecol. 2016;48:185–92.
7. Werner H, dos Santos JR, Fontes R, et al. Additive manufacturing models of fetuses built from three-dimensional ultrasound, magnetic resonance imaging and computed tomography scan data. Ultrasound Obstet Gynecol. 2010;36:355–61.
8. Werner H, Lopes J, Tonni G, et al. Maternal-fetal attachment in blind women using physical model from three-dimensional ultrasound and magnetic resonance scan data: six serious cases. J Matern Fetal Neonatal Med. 2016;29:2229–32.

U.PORTO

FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Anexos / Supplementary information

Unidade de Investigação

Tomei conhecimento. Nada a opor.

25 de Junho de 2018

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

n.º 128/18

SÃO JOÃO

DIRECÇÃO CLÍNICA

Aprovado. A.C.A. 26/6/18

(Prof.ª Doutora Ana Azevedo)

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 28 JUN 2018

Presidente do Conselho de Administração

(Dr. António Oliveira e Silva)

Diretor Clínico (Prof. Dr. José Artur Paiva) | Enfermeira Diretora (Enf.ª Filomena Cardoso) | Vogal Executivo (Dr. Luís Porto Gomes) | Vogal Executivo (Dr. Rui [illegible] Matos)

Nome do Investigador Principal:

Prof. Carla Ramalho

Título da Investigação:

Improving the diagnosis of skeletal dysplasias – a 15 year retrospective cohort reviewing concordance between sonographic, genetic and morphological feature

Pretendendo realizar no(s) Serviço(s) de:

Ginecologia e Obstetrícia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 19 *de* abril *de* 2018 .

assinatura

Centro de Investigação HSJ

RECEBI

4/6/2018

CES-IM005-0

Parecer da Comissão de Ética para a Saúde do

Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Improving the diagnosis of skeletal dysplasias - a 15 year retrospective cohort reviewing concordance between sonographic genetic and morphological feature

Nome da Investigadora Principal: Prof.ª Doutora Carla Ramalho

Onde decorre o Estudo: No Serviço de Ginecologia e Obstetrícia do CHSJ. Dispõe de autorização do Prof. Doutor Nuno Montenegro.

Objectivos do Estudo:

Estudo retrospetivo sem intervenção que tem como principai objetivos: a) avaliar a prevalência das osteocondrodisplasias (OCD) num centro hospitalar terciário; b) avaliar a taxa de sucesso diagnóstico com recurso a critérios ecográficos e comparação anatomopatológica; c) avaliar a taxa de concordância da ecografia com estudo genético e anatomopatológico e d) rever os protocolos de estudo das OCD com vista a melhorar a sua taxa de sucesso. A população do estudo será constituída por fetos em que a gravidez foi interrompida por diagnóstico de displasia esquelética no CHSJ e a quem foi realizada autópsia clínica.

Concepção e Pertinência do estudo: Os resultados do estudo poderão contribuir para um conhecimento mais atualizado sobre questões relacionadas com o diagnóstico das patologias em estudo.

Benefício/risco: Não aplicável

Confidencialidade dos dados: Está previsto o acesso a dados clínicos através da investigadora, que é médica do Serviço.

Respeito pela liberdade e autonomia do sujeito de ensaio: Face à natureza do estudo, a obtenção de consentimento informado é dispensável.

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: Dezembro de 2018

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 25 de Maio de 2018

O Relator da CES, Prof. Manuel Pestana

SÃO JOÃO

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto,

Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: Improving the diagnosis of skeletal dysplasias Ôa 15 year retrospective cohort reviewing concordanc

Nome do investigador: Carla Maria de Almeida Ramalho

Endereço eletrónico: carlaramalho@med.up.pt **Contacto telefónico:** 964883038

Caracterização da investigação:

☒ Estudo retrospetivo ☐ Estudo observacional ☐ Estudo prospetivo

☐ Inquérito ☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção ☒ Sem intervenção

Formação do investigador em boas práticas clínicas *(GCP)*: ☐ Sim ☐ Não

Promotor *(se aplicável)*: _____

Nome do orientador de dissertação/tese *(se aplicável)*: Prof. Carla Ramalho

Endereço eletrónico: carlaramalho@med.up.pt

Local/locais onde se realiza a investigação: Centro Hospitalar S„o Jo„o / Faculdade de Medicina da Universidade do Port

Data prevista para início: 2 / 5 / 2018 Data prevista para o término: 01 / 12 / 2018

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

- Calculo da prevalência das osteocondrodisplasias (OCD) num centro hospitalar terciário
- Avaliação da taxa de sucesso diagnóstico com recurso a critérios ecográficos e comparação anatomopatológica
- Avaliação da taxa de concordância da ecografia com estudo genético e anatomopatológico
- Revisão dos protocolos de estudo das OCD com vista a melhorar a sua taxa de sucesso

Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):

- Diagnóstico situacional da prevalência e a sua variação nos últimos 15 anos
- Identificação dos critérios com maior valor preditivo positivo e negativo no estudo não invasivo destas patologias.
- Aumento da taxa de sucesso diagnóstico que presentemente se situa em apenas 40% e secundariamente mais correto encaminhamento da gravidez tanto a nível de interrupção medica, preparação psicológica do casal e calculo do risco de recorrência futura.

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

Aceso limitado ao investigador e orientador do registo clínico

O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☒ Não

CONSENTI MENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☒ Sim ☐ Não

Se não, referir qual o fundamento para a isenção:

Existe informação escrita aos participantes: ☒ Sim ☐ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☐ Investigador ☐ Promotor ☐ Ambos ☒ Serviço onde é realizado

☐ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Riscos/incómodos previsíveis:

São dadas contrapartidas aos participantes:

- *pela participação* ☐ Sim ☒ Não ☐ Não aplicável
- *pelas deslocações* ☐ Sim ☒ Não ☐ Não aplicável
- *pelas faltas ao emprego* ☐ Sim ☒ Não ☐ Não aplicável
- *por outras perdas e danos* ☐ Sim ☒ Não ☐ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☐ Não

LISTA DE DOCUMENTOS ANEXOS

- [x] Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- [ ] Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- [x] Protocolo do estudo
- [x] Declaração do Diretor de Serviço onde decorre o estudo
  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- [ ] Profissional de ligação
- [ ] Informação dos orientadores
- [ ] Informação ao participante
- [ ] Modelo de consentimento
- [ ] Instrumentos a utilizar *(inquéritos, questionários, escalas, p.ex.)*: _____
- [ ] Curriculum Vitae abreviado *(máx. 3 páginas)*
- [ ] Protocolo financeiro
- [ ] Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 19 de abril de 2018

Nome legível: CARLA RAMACHO

assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP Emitido na reunião plenária da CE de ____ / ____ / ____

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

SÃO JOÃO

Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Número do Pedido
1180061910
(A preencher pelo Gabinete de Apoio ao RAI)

Exmo. Senhor
Responsável pelo Acesso à Informação
(Artigo 9.º da Lei n.º 26/2016, de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

SÃO JOÃO

AUTORIZADO
RAI - Responsável pelo Acesso à Informação no Centro Hospitalar de São João
(Art. 3º, Lei 26/2016, de 22/8)
30/5/2018

1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

1.1. Investigador Principal

Nome Carla Maria de Almeida Ramalho
Contacto telefónico
Endereço eletrónico carlaramalho @ med.up.pt

1.2. Investigador(es) Associado(s)

Número Total:

Nome Miguel Pereira da Cunha Coelho de Macedo
Contacto telefónico 912096578
Endereço eletrónico miguel_macedo2 @ hotmail.com

Nome
Contacto telefónico
Endereço eletrónico @

Nome
Contacto telefónico
Endereço eletrónico @

1.3. Afiliação Institucional do Investigador Principal

1.3.1. Grupo Profissional

- [x] Médico(a)
- [ ] Enfermeiro(a)
- [x] Docente
- [ ] Estudante
- [ ] Outro. Qual?

1.3.2. Documento de identificação pessoal ou profissional

- [ ] Cartão de Cidadão
- [ ] Bilhete de Identidade
- [ ] Célula Profissional
- [ ] Cartão de Docente
- [ ] Cartão de Estudante
- [ ] Outro. Qual?

Número de Documento

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento *Preenchimento Obrigatório*

2.1. Enquadramento da investigação

- [x] Trabalho académico de investigação e desenvolvimento:
  - [ ] Não conferidor de grau
  - [ ] Conferidor de grau: [ ] Licenciatura [x] Mestrado [ ] Doutoramento
- [ ] Projeto de investigação e desenvolvimento

RAI-IM002-0

2.2. Entidade(s) que tutela(m) a investigação

☒ Centro Hospitalar de São João

Serviço: Ginecologia e obstetricia

☒ Universidade do Porto

Faculdade / Instituto: Faculdade de Medicina

☒ Outra Instituição. *Qual?* Instituto de Investigação e Inovação em Saude

Há alguma parceria entre instituições?

☐ Não ☒ Sim. Qual(is)? Centro Univeristario de Medicina - CUME

2.3. Orientador *Se Aplicável*

Contacto telefónico

Endereço eletrónico carlaramalho @ med.up.pt

2.4. Título provisório

Improving the diagnosis of skeletal dysIpasias Öa 15 year retrospective cohort reviewing concordance between sonographic, genetic and morphological features

Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI – DAta REuse Certificate for Research – DARE através dos contactos disponíveis no fim deste formulário.

2.5. Acesso requerido

☐ Ficheiro

Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.

☒ Consulta de processos clínicos em ambiente papel:

☐ Bloco ☒ Consulta Externa ☐ Hospital de Dia ☒ Internamento ☒ MCDT ☐ Urgência

Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.

Anexar ficheiro no ato de envio

☒ Consulta de registos clínicos eletrónicos

Especificar os Sistemas de Informação:

Data previsível de fim de utilização das credenciais de acesso ☐☐☐☐ - ☐☐ - ☐☐

☐ Outro Acesso. Qual?

2.3. Pareceres e Autorizações

☒ Autorização da Hierarquia

☒ Protocolo Científico Aprovado [1]

☒ Parecer da Comissão de Ética para a Saúde (CES) [1]

☒ Parecer do Centro de Epidemiologia Hospitalar [1]

Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.

Anexar ficheiro no ato de envio

[1] *Obrigatório quando aplicável.*

3. Observações *Preenchimento Facultativo*

4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada *(n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12, ambos da Lei n.º 26/2016, de 22 de agosto)* ao submeter o presente pedido concordo e fico ainda vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Não vou elaborar registos, susceptíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Não vou elaborar, nem ficar na posse, de cópias de bases de dados utilizadas na recolha de informação;
- Comprometo-me a obter junto da Comissão Nacional de Proteção de Dados (CNPD) as necessárias autorizações, para eventuais bases de dados que venha a conceber e utilizar no âmbito da presente investigação;
- Comprometo-me a devolver ao Centro Hospitalar de São João, na pessoa do seu Diretor Clínico, as bases de dados e o resultado da investigação;
- Comprometo-me a ocultar os elementos de identificação da(s) pessoa(s) a quem os registos digam respeito, em futuras e eventuais publicações de resultados;
- Comprometo-me a consultar os processos clínicos nas instalações que me forem indicadas para o efeito;
- Comprometo-me a obter os necessários pareceres, quer da Comissão de Ética do Hospital, quer do Centro de Epidemiologia Hospitalar, sempre que necessário;
- Comprometo-me a citar as fontes sempre que publicitar o trabalho de investigação independentemente de requerer a Certidão de Reutilização (DAta REuse Certificate for Research – DARE);
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a DAta REuse Certificate for Research – DARE *Preenchimento Obrigatório*

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada; ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal; ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envia cópia do referido documento, neste caso, concluído o processo ser-lhe-á devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dê.
Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

Data 2 0 | 1 8 - 0 4 - 1 9

Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt **ou** ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 **ou** 918 880 299

SUBMETER