UPDATE IN RADIOLOGY

Usefulness of magnetic resonance imaging in the prenatal study of malformations of the face and neck

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Abstract Sonography has been the fundamental pillar of fetal diagnosis, and until relatively recently, no other valid and reliable non-invasive technique that could adequately determine fetal morphology was available. However, even after the technological advances in obstetric sonography, is still unable to detect some anomalies. One example of this shortcoming is the morphological study of the face and neck. Owing to the ossification of adjacent structures and interposition of the tongue, sonography is not accurate in the detection of some of the most common anomalies.

Enormous advances have been made in fetal magnet resonance imaging since it was first described 25 years ago. The usefulness of this modality as a tool to complement sonography in fetal evaluation is now firmly established. MRI provides useful information about orofacial anatomy, enabling accurate evaluation of both the primary and secondary palates.

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PALABRAS CLAVE
Estudio prenatal; Resonancia magnética; Anomalías congénitas; Cara

Utilidad de la resonancia magnética en el estudio prenatal de las malformaciones de la cara y el cuello

Resumen La ecografía ha sido el pilar único y fundamental del diagnóstico fetal dado que, hasta hace relativamente poco tiempo, no existía ninguna otra técnica no invasiva, válida y fiable que permitiera una correcta valoración morfológica prenatal. A pesar del gran avance tecnológico en ecografía obstétrica no todas las anomalías son visibles mediante esta técnica. Respecto al estudio morfológico de la cara, la ecografía no siempre permite valorarla correctamente, circunstancia manifiesta en la evaluación del paladar, debido a la osificación de las estructuras adyacentes y a la superposición de la lengua.

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La resonancia magnética fetal ha evolucionado considerablemente desde que se describió hace 25 años y se ha convertido en una herramienta incuestionable para la valoración fetal. Ha demostrado ser complementaria a la ecografía añadiendo información útil sobre la anatomía orofacial y permitiendo así una valoración precisa tanto del paladar primario, como del secundario.

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Introduction

The objective of prenatal diagnosis is to obtain, as far as possible, genetic, anatomic, biochemical and physiological information from the fetus and to detect any abnormalities that might have an impact in both the pre- and postnatal periods. It is equally important to provide the families with information, genetic counseling and therapeutic alternatives to any abnormality detected before birth. The prenatal morphologic study to detect possible malformations is usually performed with sonography around the week 20 of pregnancy. However, despite the great technological advances in obstetric sonography with the advent of high-frequency transducers, 3D and 4D imaging, and transvaginal sonography, the evaluation of the face and neck can be limited by interposition of the tongue and the acoustic shadowing caused by ossification of facial structures.

For years now and due to the development of ultrafast sequences, magnetic resonance imaging (MRI) has emerged as a useful and valuable modality for intrauterine study of the fetus, allowing us to confirm or rule out equivocal sonographic findings and to demonstrate anomalies not detected by sonography, which may change the prognosis of the fetal anomaly and the management of the pregnancy and delivery.1

The objective of this paper is to describe the usefulness of fetal MRI in the prenatal diagnosis of malformations of the face and neck, and to illustrate with images the most common anomalies.

Study protocol and magnetic resonance technique

At our institution, fetal MRI studies are performed after fetal sonography. When possible, MRI and sonographic studies are performed on the same week of gestation. The need to perform an MRI is decided by consensus among the clinicians who are part of the committee for prenatal diagnosis of our institution (gynecologists, pediatricians, pediatric surgeons, geneticists, pathologists and radiologists). The fetal MRI is never the initial imaging study and the radiologist is always aware of the suspected fetal anomaly and even has access to the sonograms of the expectant mother.

Mother and fetus do not receive special preparation before fetal MRI. All the MRI studies are performed on a 1.5 T superconducting system with internal gradients of 25 mT/m, and a four-element body coil. Patients are usually positioned supine and feet first to minimize claustrophobia.

In the fetal MR protocol, the images are obtained using single shot sequences based on the rapid acquisition with relaxation enhancement (SS-RARE) technique and a variation of these sequences with half-Fourier reconstruction (SS-HF-RARE or HASTE) using the following parameters: an echo spacing of 10.9 ms; echo train length: 128; bandwidth: 650 Hz per pixel; effective echo time (TEeff): 87 ms; number of excitations: 1; matrix: 240 x 256 (phase x frequency), and acquisition time: 12 s/13 sections. This sequence provides images of the fetus in all space planes with a 3–5 mm thickness with no gap between slices. Sometimes, single volumetric images are acquired using SS-RARE imaging with the following parameters: TE: 1100 ms; echo train: 240; flip angle: 180°; number of excitations: 1; matrix: 240 x 256 (phase x frequency), and bandwidth: 156 Hz per pixel. This sequence provides images of 30–80 mm thickness with an acquisition time of 4–7 s.

An initial localizer of the mother is obtained to ensure an appropriate field of view. Then, images in the coronal, axial and sagittal planes are obtained with respect to the mother’s abdomen to examine the uterine anatomy, assess the position and characteristics of the placenta, and visualize the cervix, the structures of the mother’s abdomen and the position of the fetus. Next, the fetus is imaged in the coronal, axial and sagittal planes, obtaining images from all the fetal structures in the different sequences. It is recommended to position the planes to be study on the preceding image set, thus avoiding, to the extent possible, oblique planes due to fetal motion. The examination usually requires 12–15 sequences, so it typically lasts around 25 min.

When evaluating the fetal face and neck, T2 SS-HF-RARE (HASTE) sequences are almost exclusively used. T1-weighted imaging with fast gradient echo techniques is sometimes needed. The utility of diffusion-weighted imaging has not been proven for the study of anomalies of fetal face and neck.

Normal anatomy of the fetal face and neck using magnetic resonance

For MRI evaluation of the orofacial structures, T2-weighted sequences (HASTE) are used.2 Swallowed amniotic fluid that surrounds the fetus serves as an excellent contrast medium allowing identification and delimitation of many facial structures. The palate, which can be difficult to evaluate using sonography, is seen as a hypointense linear structure separating the oral cavity from the nasal cavity on T2-weighted sequences. The sagittal and coronal planes are optimal for MR imaging of the palate. Sagittal images are useful for visualizing the tongue and pharynx (Fig. 1A). Coronal images are particularly important for visualizing the soft tissue of nose and lips (Fig. 1B) and, more posteriorly, coronal images
show the primary palate separating the oral cavity from the nasal passages (Fig. 1C). The optimal plane for visualizing the upper and lower maxilla is the axial plane (Fig. 1D). In the three space planes, the eyes appear as two round hyperintense of hyperintensity on T2 images. Anteriorly, the crystalline appears as an ovoid hypointense structure on T2 images (Fig. 1E).

Anomalies of the fetal face and neck

Cleft lip and cleft palate

They are the most common congenital anomalies of the face, affecting 1/700 newborns and are more frequent in males (1.3/1).\(^2\) Their cause is thought to be multifactorial and is related to a number of environmental factors (intrauterine infections such as rubella and toxic substances such as alcohol, tobacco, drugs and medicines), and genetic factors (syndromes and chromosomal disorders).\(^4\) The risk of associated malformations is 8% for infants with isolated cleft lip, increasing to 21% in infants with cleft lip and palate.\(^5\)

Cleft lip and cleft palate are two embryologically distinct entities. Cleft lip or fissure in lip and primary palate (area of hard palate anterior to the incisive foramen) (Fig. 1F) results from failure of one or both of the nasal prominences to fuse with the maxillary prominences during weeks 4–6 of gestation. Cleft secondary palate (posterior area of hard palate) (Fig. 1F) results from failure of the palatine shelves to fuse. Palatal shelves are two laminar evaginations of the maxillary processes that grow medially to fuse in the midline during weeks 8–12 of gestation.\(^6\)

There are different combinations of these anomalies:

Cleft lip
Cleft lip may affect only the soft tissue of the lips (incomplete cleft lip) (Fig. 2) or it may extend affecting the primary palate (complete cleft lip), but without secondary palate involvement.\(^7\) The integrity of the secondary palate is best
Figure 2  Unilateral cleft lip without cleft palate. 22-week fetus. SS-HF RARE (HASTE) images. Sagittal (A) image showing an intact palate (arrow). Coronal images of the lips (B) and axial images of the upper maxilla (C) show unilateral cleft lip (black arrows) and intact maxilla (white arrows). (D) Diagram of the anomaly.

assessed in the mid-sagittal plane (Figs. 2A, 3A and 4A). Cleft lip can be unilateral or bilateral (Figs. 3 and 4). Sometimes, the anomaly is small and the diagnosis is difficult because there can be a band of connective tissue spanning the cleft.7,8 Isolated unilateral cleft lip has an excellent prognosis and is not usually associated with other malformations.5,7

Coronal MRI is useful to visualize labial clefting (Figs. 2B, 3B and 4B) and nasal distortion (Fig. 3B). The latter finding is suggestive of a primary palate defect.9 The axial plane is useful to demonstrate the lack of continuity of the upper maxilla (Figs. 3C and 4C).10 In cases of bilateral cleft lip, in addition to the described findings, protrusion of the intermaxillary segment occurs, which at sonography is described as “premaxillary pseudomass” (Fig. 4A and D).7

Cleft palate
Cleft palate is present in approximately 80% of fetuses with cleft lip (Figs. 3 and 4).11 As previously mentioned, this type of defect is best visualized in the mid-sagittal plane (Figs. 3A and 4A). In addition, the coronal plane is useful to visualize the direct communication of the oral cavity with the nasal passages (Figs. 3D and 4D). In cases of unilateral cleft lip and palate, a contralateral deviation of the caudal portion of the nasal septum can be seen (Fig. 3C).7 This
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Figure 3  Unilateral cleft lip and palate. 22-week fetus. SS-HF RARE (HASTE) images. (A) Mid-sagittal image shows absence of palate (circle). (B) Coronal image at the level of the lips shows the cleft lip (arrow) and a subtle deformity of the nose. (C) Axial image shows the lack of continuity of the upper maxilla (arrow). (D) Coronal image at the level of the nasal cavity shows the communication between the oral cavity and the left nasal passage (arrow). (E) Diagram of the anomaly.
Figure 4  Bilateral cleft lip and palate. 24-week fetus. SS-HF RARE (HASTE) images. (A) Axial image in the midline shows absence of palate (circle) and the presence of the soft-tissue outgrowth (arrow) that corresponds to the premaxillary segment of the lip. (B) Coronal image of the fetal face at the level of the lips shows bilateral cleft lip (arrows). (C) Axial image shows the bilateral defect in the upper maxilla (short arrows) and the premaxillary pseudomass (long arrow). (D) Coronal image at the level of the oral and nasal cavities shows the communication of the oral cavity with both nasal passages (arrows). The fetus had chromosome 4 deletion (46, XY of 4q) with associated heart disease. (E) Diagram of the anomaly.
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diagnosis can be difficult when the oropharyngeal cavity is not fully filled with amniotic fluid.

Isolated cleft secondary palate without cleft lip is an uncommon anomaly most often secondary to conditions that prevent an adequate development of the palate such as tumors, macroglossia or micro/retrognathia. A distinct entity is the Pierre Robin sequence, a combination of micrognathia, glossoptosis (posterior displacement of the tongue), and cleft palate. In these patients, the structures that derive from the first branchial arch are abnormal. The primary defect is mandibular hypoplasia, with the resulting posterior displacement of the tongue, which remains high in the oral cavity preventing the fusion of the palatal shelves. Children with Pierre Robin exhibit symptoms of respiratory distress and deglution anomalies. This anomaly can appear alone or in association with syndromes such as Stickler and DiGeorge syndrome.

Central cleft lip and cleft palate

It is an entity distinct from the rest because it is part of the group of midline anomalies (in the holoprosencephaly spectrum). The mid-sagittal image demonstrates the cleft palate (Fig. 5A) and the axial and coronal images confirm the presence of the central cleft lip (Fig. 5B-D). This anomaly is often associated with chromosomal disorders.

The development of 3D technology in sonography provides better visualization of the fetal face and, in selected cases, of the secondary palate. Nonetheless, sonography still has some limitations in the evaluation of the palate due to the superimposition of the tongue and the acoustic shadow of adjacent bone. Detection rates of 16–93% have been reported for cleft palate. Unlike sonography, MRI does not have these limitations and multiple studies have corroborated that it is a useful tool in the prenatal evaluation of these malformations, providing important information for a more accurate diagnosis, not only of the orofacial anomaly, but also of other associated malformations.

The treatment of these anomalies involves postnatal surgical repair. Isolated cleft lip has an excellent prognosis. When associated with cleft palate, the technique of surgical reconstruction is complex and the risk of complications such as chronic otitis media, loss of hearing and speech impairment are common.

Future prospects include major advances in intra uterine endoscopic techniques, which will allow fetal interventions. These techniques have two major advantages: healing of the surgical wound without scar formation and bone fusion without callus formation, which will, in turn, allow a normal or better development of the maxilla.

Facial cleft

It refers to a defect of both the facial soft tissue and bone. They encompass a set of fifteen rare anomalies that Tessier defined back in 1976. This classification uses the orbit as the structure of reference. Fig. 6 shows the different types: numbers 1–6 encompass the facial defects (from a medial to a lateral position), and numbers from 9 to 14 encompass cranial defects. Numbers 7 and 8 are positioned lateral to the ear and to the orbit, respectively. Numbers 0 and 14 are midline defects, anomalies in the holoprosencephaly spectrum with severe anomalies such as cyclopia (a single central orbit), synophthalmia (fusion of the orbits), arhinia (absence of nose), or central proboscis (central facial appendix). The mildest form of midline defects is the central cleft lip. All these defects may be part of different syndromes and may be associated with cleft lip and/or cleft palate. Cases secondary to amniotic bands have also been described.

Micrognathia/retrognathia

Micrognathia refers to mandibular hypoplasia and it must be differentiated from retrognathia, where the chin has a normal size but a posterior location. Both conditions can appear together. They are present in many syndromes (Treacher-Collins, Goldenhar, Roberts) and chromosomal disorders (trisomy 9, 13 and 18). These anomalies tend to displace the tongue backward and upward, precluding a normal development of the hard palate, and the presence of an associated isolated cleft palate is not uncommon. Prognosis depends on the type of syndrome and the associated anomalies.

This anomaly is best visualized in mid-sagittal images on MRI (Fig. 7), while mandibular asymmetry is best visualized in the axial plane. The characteristic finding is the excessive upper lip protrusion over the lower lip in mid-sagittal images, due to a small mandible in a posterior position. Sonographic measurements of the fetal mandible have been widely described. Mandibular anomalies can make fetal deglutition difficult, causing polyhydramnios and incomplete stomach repletion.

Macroglossia

Macroglossia or unusual enlargement of the tongue is often part of different syndromes (Pfeiffer, Down, Hurler, Beckwith-Wiedemann). Sonographic measurements of the fetal tongue have been described. At MRI, the tongue is hypointense on T2-weighted images (Fig. 1A) and assessment of its size is often difficult.

First and second branchial arch syndromes

They encompass multiple entities secondary to first and second branchial arch anomalies such as Treacher-Collins syndrome, aurico-condylar syndrome, or oculo-auriculo-vertebral (OAV) or facio-auriculo-vertebral (FAV) syndrome. The latter being the most frequent syndrome and the one for which the usefulness of fetal MRI has been described.

Oculo-auriculo-vertebral spectrum

It consists of a group of craniofacial anomalies of multifactorial cause with an incidence of around 1/5600 newborns. They are the result of first and second branchial arch anomalies, therefore presenting with middle and external ear (preauricular appendages, anotia [absence of external ear], microtia [small external ear] and stenosis or atresia.
Figure 5  Midline cleft lip and palate. 21-Week fetus. SS-HF RARE (HASTE) images. (A) Sagittal image shows absence of palate (circle) and brain anomaly (holoprosencephaly) (arrow). (B and C) Coronal images at the level of the lips and nasal passages show the midline cleft lip (arrows). (D) Axial image at the level of the upper maxilla shows the central maxillary defect (arrow). The fetus had trisomy 13 with associated semilobar holoprosencephaly. (E) Diagram of the anomaly.
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The MRI diagnosis of these anomalies is complex, with few references in the literature.\textsuperscript{31,42} A paper on prenatal evaluation of the middle ear using MRI in OAV has been recently published.\textsuperscript{44}

Ocular anomalies

Anophthalmia refers to complete absence of the eye globe in the presence of eyelids, conjunctiva, and lacrimal apparatus. Anophthalmia can be primary (the eye never formed) or secondary (the initial development of the eye began and an insult disrupted the development leaving the infant with only residual eye tissue or microphthalmia). The primary form is usually associated with chromosomal or genetic disorders such as CHARGE, Walker-Warburg or Matthew Wood syndrome. Secondary anophthalmia is caused by infection (rubella), toxic-metabolic abnormalities, or vascular/ischemic lesions.\textsuperscript{6} Anophthalmia can be readily diagnosed by MRI. Evaluation of the crystalline and vitreous humor is also possible, allowing the diagnosis of conditions such as persistent hyaloid artery and congenital cataracts.\textsuperscript{45} As for ocular biometry, a simple technique has been described to obtain a perfect transocular plane.\textsuperscript{46} Hypertelorism (increased distance between the orbits) is present in many entities such as chromosomal disorders, frontonasal dysplasia, central facial cleft, encephalocoele or craniosynostosis.\textsuperscript{47} Hypotelorism (decreased distance between the orbits) is associated with holoprosencephaly, chromosomal disorders (especially trisomy 13) or craniosynostosis. Ocular measurements of both the orbital distance and volume have been carried out that allow objective quantification of these anomalies\textsuperscript{18,49} (Fig. 8).

Figure 6  Tessier classification of facial clefts.

of the external auditory canal, orbit (orbital dystopia [malposition of the orbits], microphthalmia and anophthalmia [absence of eye globe]), temporal bone, zygomatic arch, upper and lower maxilla. The clinical spectrum is wide, ranging from mild forms involving only the preauricular appendages to severe forms such as Goldenhar syndrome (hemifacial microsomia, epibulbar dermoid and vertebral anomalies) (Fig. 7B).\textsuperscript{44} Hemifacial microsomia, an anomaly of the OAV spectrum, is the second most common craniofacial anomaly after cleft lip.\textsuperscript{42,43} It is characterized by facial asymmetry and mandibular hypoplasia, usually unilateral.

Figure 7  Micrognathia-retrognathia. 18- (A) and 21- (B) week fetuses, respectively. (A) Mid-sagittal SS-HF RARE (HASTE) image shows a small lower jaw (arrow). Although it cannot be adequately assessed due to the gestational age, there seems to be hypoplasia of the cerebellar vermis. The fetus exhibited an akinesia–hypokinesia sequence associated with cerebral and heart malformations. (B) Sagittal SS-HF RARE (HASTE) image shows a small lower jaw. The patient had oculo-auriculo-vertebral disorder with preauricular appendices and hemivertebra, not detected by fetal MRI.
Tumors and masses

They are unusual. Fetal MRI provides information regarding the extent of the lesion, local mass effect and associated anomalies. Typically, the location, vascularity, and signal characteristics (solid, cystic or mixed) of the lesion will aid in the diagnosis. During pregnancy, these masses may interfere with fetal deglutition, causing polyhydramnios. Selective evaluation of the pharynx and trachea is required because their compression or distortion will require intensive fetal monitoring and specific surgical management during labor. The following are the most common tumors and masses.

Congenital granular cell tumor or epulis (Fig. 9)

It is a rare benign tumor that arises from the anterior maxillary ridge. They can occur as single or multiple masses and have a female predilection (1:10 ratio). Epignathus (a teratoid tumor that can protrude through the mouth) must be included in the differential diagnosis. The treatment is surgical resection. MRI shows a hypointense mass on T2-weighted images due to the fibrous component.

Vascular anomalies

They include vascular malformations and vascular tumors. Hemangioma is the most common vascular tumor. They generally appear in the first year of life and involute over a period of years, but in some patients, hemangiomas are present at birth. These lesions, known as congenital hemangiomas, grow during fetal development and have grown to its maximum size at birth. They can be classified as rapidly involuting congenital hemangioma (RICH), the most frequent, and as non-involuting congenital hemangioma (NICH). The most common locations are head, neck and extremities. Prenatal MRI demonstrates well-defined solid masses with mild heterogeneity and signal intensity ranging from hyperintense to hypointense in relation to the brain gray matter on T2-weighted sequences. Hyperintensity on T1-weighted images suggests intralesional bleeding. The detection of flow voids is indicative of their hypervascularity. In large tumors, the presence of arteriovenous shunts may result in hemodynamic changes, with jugular distension due to flow arterialization, dilation of the right heart chambers, tricuspid insufficiency and polyhydramnios. Attention should also be paid to possible associated arterial and cortical malformations of the brain (PHACES). RICHs involute completely within 12–14 months without sequelae, but they may leave residual large veins in the subcutaneous tissue or atrrophic skin. Differential diagnosis of NICH must include congenital fibrosarcoma. Other much more uncommon vascular tumors are hemangioendothelioma, hemagiopericytoma and angioblastoma.

Lymphatic malformations

They are typically known as lymphangiomas or cystic hygromas and they refer to dilated dysplastic lymphatic channels with cyst formation, accounting for 6% of all benign pediatric tumors, with 75–80% located in the head and neck. In 10% of cases, there is intrathoracic extension. Spontaneous regression of lymphangiomas occurs in 10–15% of patients. MRI reveals well-defined cystic masses with hypointensity on T1 and hyperintensity on T2. Change from a unilocular to multilocular pattern has been described as characteristic of lymphatic malformation. They are usually diagnosed in the second-third trimester of gestation and should not be confused with the posterior nuchal translucency of the first trimester. Typically, the treatment consists of complete surgical resection, but this may be challenging given the infiltrative nature of the lesion. New treatments involving intrauterine injection of sclerosing agents, such as OK-432, are being tested with good results.
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Goiter
The enlargement of the thyroid gland can be secondary to both hypo- and hyperthyroidism. The thyroid function of fetuses of mothers with Graves' disease is abnormal in 2–12% of cases. MRI shows hypointense masses on T2 and hyperintense on T1-weighted images. L-T4 has been administered into the amniotic fluid with good results.

Teratoma (Fig. 10)
Teratomas form the most common congenital tumors and, after the sacrococcygeal location, the head and neck is the second most common location. They appear as well-defined heterogeneous masses with solid and cystic components that arise from the palate, nasopharynx and thyrocervical region. MRI shows masses with hypo- and hyperintense components on T2-weighted sequences. The differential diagnostic of predominantly cystic teratomas includes intestinal duplication cysts and lymphatic malformations, more frequently located in the posterior region, while teratomas are locate anteriorly. The differential diagnosis of solid teratomas includes the congenital infantile fibrosarcoma.

Soft-tissue tumors
These tumors include myo/fibromatosis, fibrous hamartoma, rhabdosarcoma, PNET, rhabdoid tumor and congenital infantile fibrosarcoma. The latter being the most common, despite its extreme rarity, and is usually located in the

Figure 9  Epulis. 29-week fetus. (A and B) Sagittal SS-HF RARE (HASTE) images show a mass protruding through the mouth that seems to arise from the upper maxilla (arrows). Although the stomach appears normal (asterisk in B), there seems to be some difficulty with deglutition since there is polyhydramnios (black dot in B).

Figure 10  Cervical teratoma. 34-week fetus. SS-HF RARE (HASTE) images. (A) Coronal and (B) axial fetal images show a solid-cystic mass on the left side of the neck (arrows). The image also demonstrates the lesion compressing the trachea, which remains patent (arrowhead). Mid-sagittal image (C) shows a patent trachea along its course (arrows). Imaging and pathologic studies performed after birth confirmed the diagnosis of cervical teratoma.
extremities, but there are reported cases of head and neck location.75

Conclusions

Fetal MRI has developed rapidly over the last 25 years, turning from a research tool to a key component of the routine clinical practice in many institutions all around the world. Its ability to detect complex anomalies affecting different organs has been widely described, and it has become an essential technique in cases that require specific fetal assessment. Its use should be limited to specialized centers with qualified staff and under no circumstances must be considered as a substitute of sonography, which remains the technique of choice for the study of fetal morphology. Imaging diagnosis of anomalies of the fetal head and neck has progressed in line with MRI development, allowing for an adequate evaluation of these structures in the early stages of gestation. Advances in MRI, with the advent of new sequences and techniques, encourage the development of future prospect for diagnosis that will provide deep and global insight of the anomalies of the head and neck. Specialization training in prenatal imaging for radiologists will entail a higher diagnostic accuracy, which will affect prenatal counseling and will enable a better management of pregnancy and delivery.

Authorship

1. Responsible for the integrity of the study: AZC and CMM.
2. Conception of the study: AZC and CMM.
3. Design of the study: AZC and CMM.
4. Acquisition of data: CMM and AZC.
5. Analysis and interpretation of data: CMM and AZC.
6. Statistical analysis: N/A.
7. Bibliographic search: AZC and CMM.
8. Drafting of the paper: AZC and CMM.
9. Critical review with intellectually relevant contributions: CMM.
10. Approval of the final version: AZC and CMM. All the authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare not having any conflict of interest.

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