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Prenatal cerebral magnetic resonance imaging

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ABSTRACT

Ultrasonography (USG) is the preferred screening method for fetal brain examination. It has some technical limitations and a relatively low sensibility and specificity for many central nervous system (CNS) malformations. Fetal cerebral magnetic resonance imaging (MRI) offers better resolution and sensibility, with scarce limitations.

Objectives: To determine the fetal age according to cortical maturation as seen in MRI, correlating these data with those obtained by means of USG measurements; to correlate USG pathological findings with the MRIs and to determine how the sequence of cortical maturation varies in abnormal brains.

Materials and methods: 50 pregnant women were submitted to USG and fetal brain MRI. Fifteen carried out normal pregnancies. In the remaining 35, the USG, the clinical assessment or both, raised the suspicion of a CNS malformation. Facts studied were: the gestational age calculated by USG, analysis of the cortical gyral development by MRI (cortical age), the presence of CNS abnormalities and the correlation between the cortical maturation and the presence of CNS pathologies. Statistical analysis included the Student's *t* test for paired samples, the Pearson's correlation coefficient (*r*) and linear regression curves.

Results: In the control group, fetal age highly correlated with the cortical age estimated by MRI. In the abnormal group, a wide variety of pathologies could be found, with higher sensibility and specificity than USG when applying MRI techniques. Cortical age did not correlate with the gestational age in this group; moreover, its estimation could not be achieved in severely malformed brains.

Discussion: MRI allows a detailed study of the CNS before birth. It proved to be more reliable and specific than USG, with fewer technical limitations. Cortical maturation can be accurately assessed by this method in normal or slightly abnormal fetuses. However, USG is better than MRI for diagnosing skull bony defects.

1. Introduction

Congenital brain malformations are numerous; more than 2000 different congenital cerebral malformations have been described. Two thirds of the major embryological anomalies affect the central nervous system (CNS) [1,2]. Some of them can be diagnosed prenatally by means of ultrasonography (USG), which is the current technique usually employed for routine examination of the fetal brain during pregnancy, due to its capacity for acquiring reliable and inexpensive images at real time.

However, when a brain abnormality is detected by USG, its prognosis may not be related solely to the observed anomaly, but by the presence of other eventual associated CNS malformations as well, which may escape its detection by this method. For instance, an isolated ventriculomegaly (congenital hydrocephaly) has better prognosis than any other which is associated with other CNS malformations. The incidence of isolated ventriculomegaly employing USG is as much as 84%, while when magnetic resonance imaging (MRI) is used it falls to 42% [1,2,13,15]. The rate of survival for fetuses with isolated ventriculomegaly is 80%, however only 50% of them will have a normal neurological development. Besides, USG may have technical limitations, such as maternal obesity or oligoamnios, both of which diminish even more its relatively low sensibility [1,2,15].

Fetal cerebral MRI, a relatively new technique, offers multiplanar capacity, a better resolution and higher sensibility. Nevertheless, it has some limitations; it is useful only after 17–18 weeks of pregnancy, since images of good quality are difficult to obtain in smaller fetuses. Some fetal positions may also disrupt the quality of the images; better images are usually achieved with fetuses in cephalic presentation,

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Table 1
Cortical age estimations employing MRI

	Sulci	Weeks of first appearance
Medial surface	Parietoocipital s.	≤20
	Calcarine s.	≤20
	Cingular s.	≤20
Basal surface	Hippocampic fiss.	20–23
	Collateral s.	20–23
Lateral surface	Lateral s.	<20
	Superior Temporal s. (anterior half)	24–27
	Superior Temporal s. (posterior half)	20–23
	Inferior temporal s.	28–31
	Insular sulci	32–35
Vertex	Central s.	20–23
	Precentral s.	24–27
	Postcentral s.	24–27
Secondary sulci		32–35
Tertiary sulci		36–39

while in podalic presentation, images may be disturbed by fetal head movements accompanying the maternal breathing [1,2,15].

The present work is a multicentric experience employing MRI for intrauterine brain examination. It is in line with a previous study, in which the appearance of the fetal brain, at different stages of gestation, was analyzed in postmortem normal fetal brains, employing MRI and anatomically dissecting them [3].

The goals of this study are: a) to determine the fetal age according to cortical maturation as seen in MRI, correlating these data with those obtained by means of ultrasound measurements, b) to correlate pathological findings seen in USG with the MRIs, and c) to determine how the sequence of cortical maturation varies when cerebral pathology is present.

2. Materials and methods

By means of an agreement amongst FEMIEN Foundation, the Ramos Mejía Hospital and the Sardá Maternal Hospital, 50 women with 20 or more weeks of pregnancy were selected for this study. All of them signed an informed consent before being submitted to the test. The research protocol was approved by the ethical committees of the three institutions.

Fifteen women carried out normal pregnancies; in the remaining 35, either the USG or the clinical assessment, or both of them, raised the suspicion of a possible CNS malformation. A fasting period of 6 h before the acquisition of images was required in all of them, to minimize fetal movements.

Gestational age was calculated by the usual ecographic measurements (biparietal diameter [BPD], femoral longitude, and abdominal circumference). The USG operator was always the same person.

MRIs of the fetal brains were performed in ultra-fast sequences (T1 and T2 TSE), without gadolinium, in sagital, coronal and axial slices, plus a sagital slice including the whole spine and axial slices at the lumbar spine. In addition to the standard body coil, another one was placed at the pelvis. To improve the definition of the image two saturation bands were added (one in the subcutaneous fat of the mother's abdomen and other at the bottom of the back). The time elapsed between the USG, which always was performed first, and the MRI studies was considered, adding the days including within the time gap to the ecographic calculation of fetal age. Later, two different observers (MB and CR), blinded to each other, without knowledge neither of the gestational age nor of the clinical records and the USG diagnosis, analyzed the fetal MRIs estimating the fetal age according to the maturation of the cortical gyri and sulci (cortical age, see Table 1). The normal cortical development can be easily recognized in fetal brain MRIs. Sulcal and gyral maturation follows a precise and predetermined sequence that has been extensively studied either in vitro, by MRI or employing both methods [1–3,7,12,1 20,23]. This cortical morphological analysis allows calculating the fetal age with an error that fluctuates between 1 and 2 weeks, as other embryological methods. The presence of malformations and/or destructive lesions was assessed by this technique as well.

Data obtained were divided into two groups, one which was called control, encompassing normal fetuses, and other composed of abnormal fetuses. One of the pregnant women showed in two USG examinations carried out in different centers, and by different operators, a fetus with a brain tumor that could not be found in MRIs performed pre and postnatally, so she was included into the control group.

Variables studied for further statistical analysis were: a) the gestational age calculated by USG, b) analysis of the cerebral cortical gyral development by MRI, examining the lateral, medial and basal surfaces and the vertex, to calculate the cortical age, c) the presence of CNS abnormalities, in every case USG findings were correlated with those obtained by MRI, settling down the frequency of each pathology for each technique, and d) the correlation between the cortical

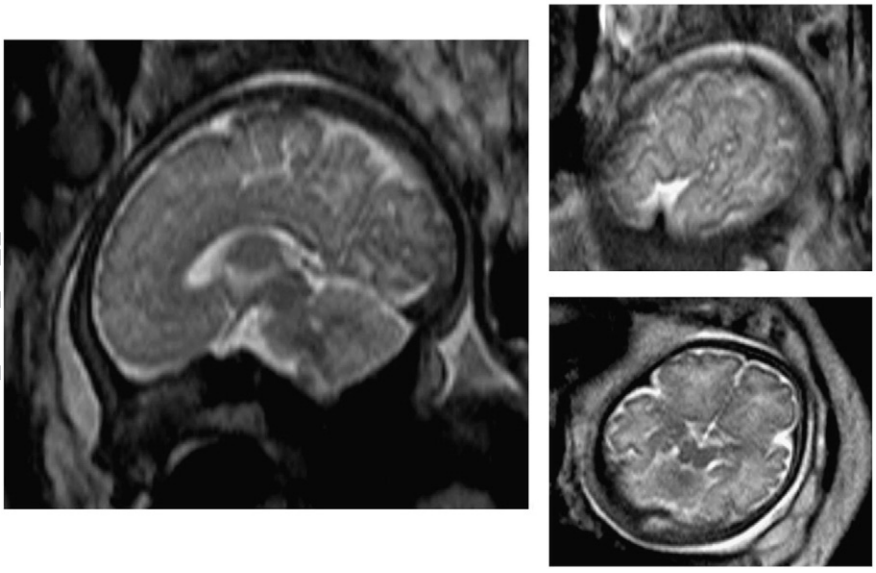

Fig. 1. Normal fetal brain at 38 weeks of gestation. Sagital and axial slices at T2 sequence.

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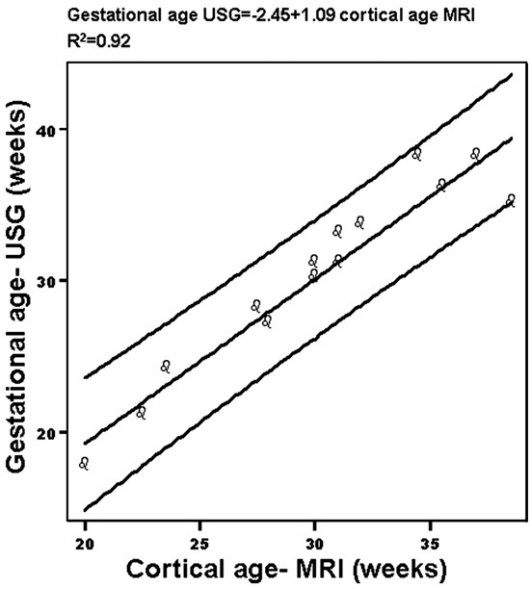

Fig. 2. Linear regression curve in normal brains, correlating the gestational age measured by US with the cortical age estimated by MRI.

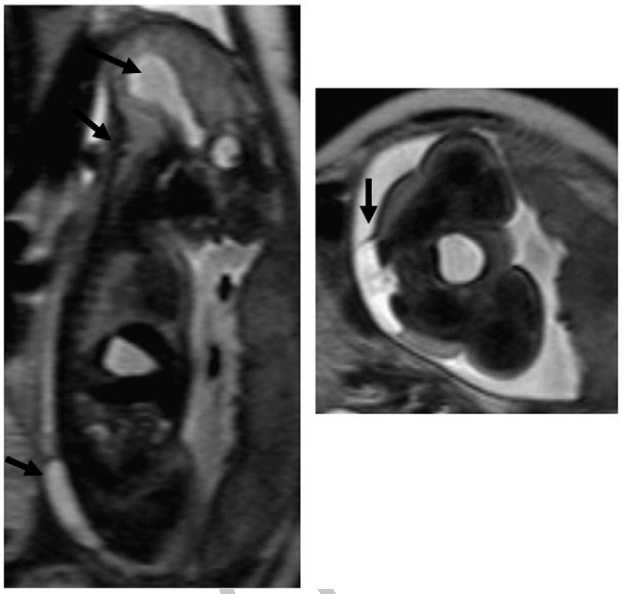

Fig. 4. Hydrocephalus associated to Chiari II malformation with myelomeningocele (arrows) in a fetus of 31 weeks of gestation. Sagital slice encompassing the whole spine (right), axial slice at the lumbar spine (up), T2 sequence.

maturation and the presence of CNS pathologies. In cases of agenesis of the corpus callosum, the cingulate sulcus was not included in the analysis.

The following statistical tests were used: the Student's *t* test for paired samples and the Pearson's correlation coefficient for comparison between 2 variables. It was considered as statistically significant if a p value ≤ 0.05. A linear regression curve was drawn in both groups comparing the aforementioned variables.

3. Results

3.1. Control group ($n=15$)

The subjects included within this group were women whose pregnancy times varied between 18 and 39 weeks (mean 33 +/− 2 weeks) (Fig. 1). Fetal age in this group, estimated by USG, highly correlated with cortical age calculated by MRI ($r=0.96$, $r^2=0.92$ $p<0.759$) (Fig. 2).

3.2. Abnormal group ($n=35$)

This group encompassed 35 women whose pregnancy times varied between 19 and 40 weeks (mean 30. 58 +/− 2 weeks)(Figs. 3–5).

The correlation between the gestational age, as estimated by USG, and the cortical age, as calculated by MRI was not significant in this group ($r=0.40$, $r^2=0.17$; $p=0.005$) (Fig. 6). In most cases, the *cortical age* was delayed 2 or more weeks. In the presence of more severe malformations, some sulci seemed not to be developed at all.

USG diagnosis in most of these patients ($n=19$) was isolated ventriculomegaly. However, within this subgroup MRI showed isolated ventriculomegaly only in 6 patients, while the remainder 13 associated other brain malformations or destructive lesions. Additional MRI findings included Arnold–Chiari type II malformations, myelomeningocele, agenesis of the corpus callosum, enlarged magna cistern, and semilobar holoprosencephaly (see Table 2).

In one fetus, MRI showed a complex cerebral malformation combining microcephaly, hypoplasy of the falx cerebri and the frontal lobes, a severely dysplasic cortex with heterotopias and an extremely poor gyral development. The ventricular system was severely dysmorphic, and the right occipital lobe was displaced to the left hemicranium. This case also had a severe skull defect that was not detected by the MRI, despite being accurately diagnosed by USG. This fetus died a few days after delivery. The pathological analysis confirmed the cranial defect that showed the ultrasound and the deep parenchymal malformations depicted by the MRI.

In all those fetuses showing congenital hydrocephaly, cortical sulci and gyri were flattened, mainly at the convexity and, particularly, at the posterior areas. This made the estimation of the *cortical age* extremely difficult, because it was almost impossible to recognize the

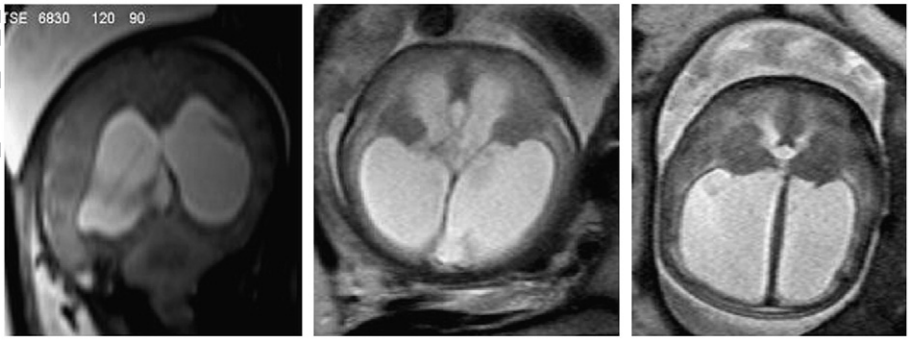

Fig. 3. Several cases of ventriculomegaly, all of them in the third gestational trimester. Note the lack of cortical development and sulcation. Axial slices in T2 sequence.

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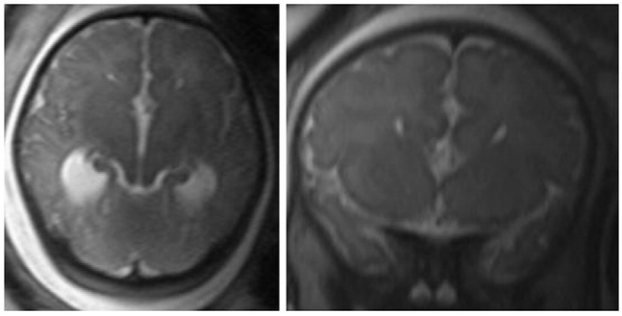

Fig. 5. Isolated agenesis of the corpus callosum. 31 weeks of gestation. (axial (up) and coronal (down) slices, T2 sequence).

main cortical landmarks. Some less severe cases, however, had a rudimentary sulcal development at the base of the brain. Those sulci, nevertheless, were not accurately developed regarding their real gestational age.

4. Discussion

Despite its numerous advantages (low cost, common availability, noninvasive character), USG has some limitations, due to the non-specific appearance of several anomalies and technical factors that may not allow a correct visualization of the CNS. Moreover, USG often fails to visualize some parenchymal anomalies. All those difficulties are solved by means of the MRI.

This last technique proved to be a highly effective tool for the detailed intrauterine study of the fetal brain. In normal fetuses within our material, the sequence of cortical maturation could be described. Good correlation with routine ultrasound measurements currently employed for fetal age estimation was found. Under these circumstances, both techniques appear equally reliable.

The group of abnormal fetuses showed a high frequency of ventriculomegaly. MRI depicted that most of them were associated with other CNS malformations, which change the prognosis dramatically [1,2,13]. As it has been proposed by Girard et al. [13], MRI should be a primary tool in the work-up of ventriculomegaly because of its crucial role in detecting other CNS anomalies that fall beyond the scope of USG. In hydrocephalic brains sulcal and gyral development

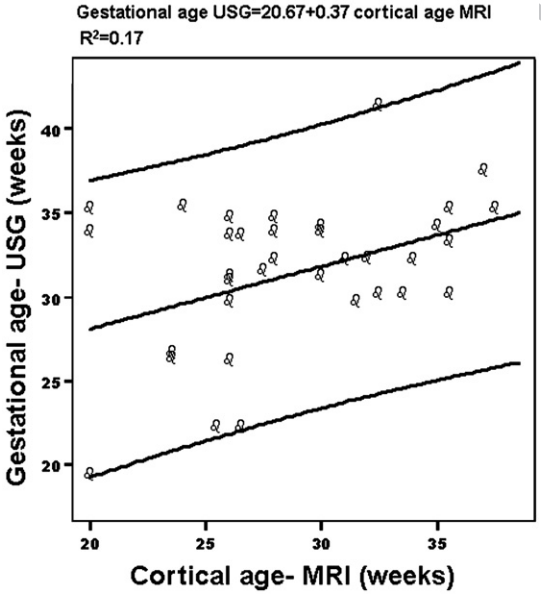

Fig. 6. Linear regression curve in abnormal brains, correlating the gestational age measured by US with the cortical age estimated by MRI.

Table 2
Ultrasound and MRI findings in the abnormal group

USG finding	MRI finding	*n*	
Ventriculomegaly (*n*=19)	Ventriculomegaly	19	
		Isolated: 6	Associated to other malformations: 13
	Arnold–Chiari II	8	
	Destructive lesions	4	
None (*n*=15)	Myelomeningocele	8	
	Agenesis of the corpus callosum	4	
		Isolated: 2	Associated to other malformations: 2
	Semilobar holoprosencephaly	3	
Skull defect (partial anencephaly) (*n*=1)	Complex brain malformation	1	
None (*n*=2). Cystic malformation of the posterior fossa (*n*=1)	Enlarged cisterna magna	3	

could not be evaluated properly, because the landmarks of cortical development are unreliable in the grossly malformed brain. Many of the sulci had probably disappeared as a result of deformation by the mass effect. Even more, most of them did not develop at all; the scarce sulci found in these cases had a poorer maturation grade than the expected. It has been described in the literature [1,2,7,13,15,16]. that normal maturation is delayed in brains with pathology. Slagle et al. [20] hypothesized that alterations in local nutrients might result in decreased cellular proliferation and delayed sulcal development. There may be many other reasons accounting for this delay, for example, the "inside-out" pressure gradient coming from the dilated ventricles might have an hydrodynamic effect opposed to the "outside-in" folding force vectors. Nevertheless, even in isolated ventriculomegalies, without mass effect, cortical development is slightly delayed. Perhaps the same noxious stimulus may simultaneously cause ventricular dilation and a disruption or a delay in the process of cortical folding.

Regarding the aforementioned findings it might be interesting to search what would happen with the development of those sulci and gyri if the ventricular dilation could be reverted on time. If the ventriculomegaly is, somehow, at least partially responsible for the delayed development of the cerebral cortex, the prognosis would be better. Further studies are also necessary to identify whether those fetuses with delayed cortical maturation associated to mild ventriculomegaly are those who later, as children, will have developmental delay. Several studies analyzing the natural history of fetal hydrocephaly and animal experiments have unanimously shown that the earlier the treatment, the better the results, from both motor and itive points of view [4–6,9–11,17,19,21,22,24].

In many cases in which USG made the diagnosis of isolated ventriculomegaly, MRI showed posterior fossa malformations (Chiari II). In other cases, USG showed nonspecific cystic images in the posterior fossa, but MRI allowed an excellent visualization of those structures. MRI was more efficient than ultrasound in evaluating the brain state at the posterior fossa.

However, MRI was not as useful for the visualization of bony structures as USG was, as proved case no. 3, a fetus showing extended skull abnormalities which were well seen employed USG and unable to be depicted by MRI.

The importance of the early detection of a CNS malformation is directly related to an eventual prenatal neurosurgery. Many fetal malformations incompatible with life are now candidates for surgical treatment intra uterus. Other not lethal malformations, as neural tube closing defects, are being repaired intra uterus in some centers, with a significant decrease in the incidence of shunt-dependent hydrocephalus among newborn infants [4–6,9,11,17,21,22]. The fetal brain has an unique capacity of recovery from the insults [21]. Therefore, an early surgery could avoid the progressive damage caused by an active

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pathology. However, for the most frequent abnormality, hydrocephalus, with an incidence of 0.3–2.5/1000 newborns, fetal neurosurgery have shown contradictory results, so far [5,6,9,11,17,21]. Perhaps one of the reasons accounting for some of these failures were the inadequate selection of the patients, based in many cases only in USG images, a technique which, as shown by this work and others [1,2,13,15] underestimates the presence of accompanying malformations which could be easily identified by MRI. Another explanation may be related to the timing of the surgery: As animal studies have shown, if it is performed later in the course of the pregnancy, the chance of a normal cortical development is quite smaller.

In summary, MRI allows a detailed study of the CNS before being born from relatively early periods of the gestation. It proved to be more sensitive and specific than USG, and its technical limitations are scarce. Cortical maturation can be accurately assessed by this method in normal or slightly abnormal fetuses, highly correlating with USG measurements.

The fact that, nowadays, it is possible to detect and to treat CNS anomalies precociously, improving the prognosis and the quality of life of these small patients and their families, make this technique a new field of fascinating research, with potential possibilities which warrants further investigations.

5. Uncited references

[8]
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