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REVIEW ARTICLE

Journal Watch

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Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. Griffiths PD, Bradburn M, Campbell MJ, Cooper CL, Graham R, Jarvis D, Kilby MD, et al.; MERIDIAN collaborative group. Lancet. 2016 Dec 14. pii: S0140-6736(16)31723-8. doi:10.1016/S0140-6736(16)31723-8. [Epub ahead of print].

Fetal brain abnormalities occur in approximately 3 in 1000 pregnancies and fetal imaging with ultrasonography has been the mainstay and first level of investigation for many years. Previous studies have suggested that in utero MRI (iuMRI) might be useful as an adjunct to ultrasound for detecting brain anomalies, but uncertainty remains regarding the extent of diagnostic and clinical impact.

This prospective, multicenter, cohort study was aimed at providing information on diagnostic performance, clinical impact and patient acceptability of iuMRI. Pregnant women aged 16 years or older whose fetus had a brain abnormality detected by ultrasound at a gestational age of 18 weeks or more were considered eligible and had a iuMRI done within 14 days of ultrasound. The cohort was subdivided by gestation into two subgroups: 18–24 weeks (n = 369) fetuses, which represented the subgroup of specific interest, and ≥24 weeks fetuses (n = 201). Gold standard for outcome was the neuroanatomical diagnosis from postnatal neuroimaging studies done up to the age of 6 months, or autopsy/postmortem MRI in case of pregnancy termination, stillbirth or neonatal death. The authors assumed that ultrasonography would achieve an accurate and complete diagnosis of brain abnormalities in 70% of cases and tested the hypothesis that it would increase to at least 80% with iuMRI, with iuMRI and ultrasound being concordant (correctly and incorrectly) in 70% of cases overall.

In-utero MRI increased the diagnostic accuracy by 23% (95% CI 18–27) in the 18–24 weeks group and by 29% (95% CI 23–36) in the ≥24 weeks ($p < 0.0001$ for both groups). The overall diagnostic accuracy was 68% for ultrasound and 93% for iuMRI (difference 25, 95% CI 21–29). The proportion of high confidence diagnoses increased by 13% after iuMRI (from 82 to 95%) and there were fewer high confidence but incorrect diagnoses after iuMRI than ultrasound (6 vs. 22% of the total number of cases), limiting the possible inappropriate change of management in these cases.

In-utero MRI was considered to provide additional diagnostic information in 49% of cases by the referring fetal medicine expert and to change itself the prognostic information in at least 20% of cases. Of note, the contribution of the iuMRI to the final choice of management was felt by the clinician to be "significant" in 26% of cases, of "major influence" in 6% of cases and "decisive" in 3% of cases. Furthermore, the overall acceptability of the iuMRI was high, with at least 95% of women saying they would undergo an iuMRI study in a future pregnancy, if needed. In contrast to previous studies and systematic reviews, this study has a prospective design, is appropriately powered and does not exclude any type of fetal brain abnormality. Even if it has to be noted that the expertise of the MRI radiographers doing the examinations is likely to have contributed to the high completion rate of iuMRI, this study clearly indicates that iuMRI improves the diagnostic accuracy and confidence for fetal brain anomalies. This leads, in turn, to prognosis and management changes in a high proportion of cases. This

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findings, along with the high patient acceptability, lead to the proposal that any fetus with a suspected brain abnormality on ultrasound should have iuMRI to better counsel the patients and guide management.

Prenatal findings in children with early postnatal diagnosis of CHARGE syndrome. Busa T, Legendre M, Bauge M, Quarello E, Bretelle F, Bilan F, et al. Prenat Diagn. 2016 Jun;36(6):561-7. doi:10.1002/pd.4825. [Epub 2016 May 12].

CHARGE syndrome is a multiple congenital anomaly syndrome characterized by the association of the following main features: ocular coloboma (C), heart disease (H), choanal atresia (A), retardation of growth and/or development (R), genitourinary defects and/or hypogonadism (G), and ear anomalies with or without deafness (E). Estimated incidence varies from 1/8500 to 1/15,000 live births. This syndrome is known to be caused by autosomal dominant mutations in CHD7, which is currently the only gene found to be associated with the syndrome and is found in 90–95% of patients with a clinical diagnosis. In the majority of cases the mutation is *de novo*. Neonates with CHARGE syndrome often have multiple life-threatening medical conditions, and brainstem and cardiac dysfunction are a major cause of morbidity. Nevertheless, the diagnosis is extremely challenging antenatally and is rarely established in utero. The aim of this study was to report data regarding pregnancy of children born with CHARGE syndrome and severe neonatal presentation, in order to improve in utero diagnosis and neonatal management.

Prenatal findings of 12 children with CHARGE syndrome diagnosed in the first 3 months and with a confirmed CHD7 mutation testing were collected. Authors retrieved data on prenatal ultrasounds (US), fetal supplementary investigations (echocardiography, fetal brain magnetic resonance imaging and fetal karyotyping) and results of postnatal evaluation.

CHARGE syndrome was suspected in three fetuses but could not be confirmed despite additional examinations. Fetus 1 presented the association of unilateral cleft lip and intrauterine growth restriction (IUGR) and external ear anomalies. In fetus 2, atrioventricular septal defect (AVSD), dilated ureters, and external ear anomaly were diagnosed. Choanal atresia was also suspected. Fetus 3 had bilateral cleft lip. In four other patients, US survey showed various congenital malformations, but CHARGE syndrome was not suspected before birth. In the five remaining patients the prenatal US assessment was considered normal.

Clinical diagnosis was made at birth in 10 babies. Ten out of the 12 babies (83%) needed supportive care during the neonatal period. The mortality was 57% (4/7) in the group with abnormal findings during pregnancy and 20% (1/5) in the group with normal prenatal findings.

Congenital heart disease (CHD) was present in 10 out of 12 babies (83%), which is consistent with data from the literature (74–76%). Nevertheless, excluding patent ductus arteriosus (PDA) that is overrepresented in CHARGE syndrome (which by definition, cannot be diagnosed during pregnancy), only four children were affected by CHD (33%) in the present series. Of these, two were diagnosed in utero (one tetralogy of Fallot and one AVSD) and two after birth (one atrial septal defect and one aortic coarctation). Among other major features of CHARGE syndrome, ocular coloboma, choanal atresia, malformed external ears, cleft lips, arhinencephaly, and semicircular canal agenesis are potentially detectable in utero with scans and/or fetal MRI. Ocular coloboma was present in all but one children at birth, was never detected in utero. Interestingly, two newborns had severe microphthalmia in addition to the coloboma, and this finding is potentially detectable antenatally. Intrauterine growth restriction complicated two pregnancies and is thus compatible with the diagnosis. In addition, four fetuses in the series had 22q11.2 deletion screening in utero, since many findings can overlap with this syndrome. Therefore, authors proposed that CHARGE syndrome should be considered in fetus presenting with the association of CHD and thymus agenesis and normal 22q11.2 deletion screening. Validation of CHARGE syndrome diagnosis by CHD7 screening is feasible in utero if the diagnosis is suspected. Most mutations are truncating, missense mutations are less frequent, and large deletions, accessible to array-CGH, are rare. Therefore, array-CGH does not allow CHARGE syndrome diagnosis in the majority of cases.

In conclusion, diagnosis of CHARGE syndrome remains difficult during pregnancy. If the suspicion of CHARGE syndrome is raised in utero, a careful ultrasound examination is recommended to identify external ear deformities, choanal atresia, or microphthalmia. Fetal brain magnetic resonance imaging can be helpful, but a normal result does not exclude the diagnosis. When CHARGE syndrome is highly suspected, CHD7 molecular analysis should be considered to confirm the diagnosis.

International standards for symphysis-fundal height based on serial measurements from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: prospective cohort study in eight countries. Papageorghiou AT, Ohuma EO, Gravett MG, Hirst J, da Silveira MF, Lambert A, et al.; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). BMJ. 2016 Nov 7;355:i5662. doi:10.1136/bmj.i5662.

Assessment of fetal growth is one of the cornerstones of antenatal care, in order to identify small and large for gestational age fetuses at increased risk of perinatal

morbidity and mortality. In low risk pregnancies, serial measurement of symphysis-fundal height (SFH) is widely recommended as a simple, inexpensive, first level screening tool and very often is the only available technique to assess fetal growth in low income settings. The sensitivity of SFH measurement to detect small for gestational age fetuses shows a wide variability, ranging from 17 to 93%. There is also marked study heterogeneity mainly due to the variety of methods used, including varying thresholds for defining small for gestational age and the use of multiple SFH charts. Therefore, the aim of this study was to create international symphysis-fundal height standards derived from pregnancies of healthy women with good maternal and perinatal outcomes, in order to improve the care offered to women worldwide. INTERGROWTH-21st was a multicentre, multiethnic, prospective longitudinal observational population study, conducted between 2009 and 2014 in eight countries (urban areas in Brazil, China, India, Italy, Kenya, Oman, UK, and USA). Healthy women with a naturally conceived singleton pregnancy, and who met the individual inclusion criteria, were prospectively recruited. Gestational age was estimated on the basis of the last menstrual period provided that the date was certain, and the menstrual age agreed (within 7 days) with a standardized measurement of fetal crown rump length at 9 + 0–13 + 6 weeks' gestation. Symphysis-fundal height was measured every 5 weeks from 14 weeks' gestation until birth using standardized methods and dedicated research staff that was blinded to the symphysis-fundal height measurements by turning the tape measure, such that numbers were not visible during examination. Pregnancies complicated by fetal death or congenital abnormality, catastrophic or severe medical conditions were excluded. Maternal smoking also represented an exclusion criterion. The best fitting curve was selected using second-degree fractional polynomials and further modelled in a multilevel framework to account for the longitudinal design of the study.

13,108 women were screened in the first trimester and 4607 (35.1%) met the study entry criteria. Of the eligible women, 4321 (93.8%) had pregnancies without major complications and delivered live singletons without congenital malformations. Symphysis-fundal height measurements increased almost linearly with gestational age. Data were used to determine fitted 3rd, 50th and 97th centile curves, which showed excellent agreement with observed values. Analysis of the duplicate SFH measurements obtained from all women showed that the 95% limits of agreement were about 1.5 cm.

These international, prescriptive standards, which describe optimal growth, have the potential to improve pregnancy outcomes by reducing the wide range in sensitivity for the detection of small for gestational age. Therefore, the use of the new international SFH standards in combination with standardized measurement methodology to unify and improve clinical practice is highly recommended. Printable chart is available online at https://intergrowth21.tghn.org/under "INTERGROWTH Standards & Tools".