Ultrasound Obstet Gynecol 2017; **49**: 287–288
Published online 27 November 2016 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17324

CONSENSUS STATEMENT

ISUOG consensus statement on current understanding of the association of neurodevelopmental delay and congenital heart disease: impact on prenatal counseling

An association between congenital heart disease (CHD) and neurodevelopmental delay (NDD) has long been recognized, but remains poorly understood. It is almost certainly multifactorial[1–8]. A number of abnormal magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) or sonographic findings, specifically abnormal or delayed sulcation, reduced brain biometry and volumes and abnormal brain biochemistry, have been described in fetuses and neonates with some forms of CHD[9–17]. This suggests that genetic factors[3] and the prenatal environment play an important role in the determination of postnatal neurodevelopmental function, in contrast to traditional concepts attributing adverse neurodevelopmental outcomes to postnatal events such as perinatal hypoxia and perisurgical damage. Furthermore, some large cohort trials have demonstrated an increased risk of NDD mainly – but not only – in children and young adults with univentricular circulation and, to a lesser extent, in those with transposition of the great arteries (TGA)[14,18–21]. The increasing supportive evidence in this field has led to the publication of an official scientific statement by the American Heart Association[22], in which the conclusions are that: 'Children with CHD are at increased risk of developmental disorder or disabilities or developmental delay' and, therefore, '. . . surveillance, screening evaluation and re-evaluation during childhood' are recommended to diagnose and, if possible, treat the various aspects of these disabilities.

Experience in the interpretation of any prenatal imaging modality is paramount in assessing its ability to detect real disease and, hence, its true clinical importance. This can be gained only in the setting of well-designed studies. Furthermore, the full extent of clinically important NDD cannot be determined during the first years of a child's life; thus, these studies also require adequate follow-up. The deficiencies in current published studies have raised genuine and widespread concerns that a discussion of possible adverse neurodevelopmental outcomes linked to CHD may lead couples to opt for termination of pregnancy in those cases of isolated CHD that are usually associated with low mortality and low long-term morbidity, such as TGA. However, the available evidence would suggest that it is neither possible nor ethical to ignore this risk during prenatal counseling[14,17,23].

A recent survey, conducted by an ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) Task Force to gauge the attitudes and perceptions of health professionals from leading referral units for CHD worldwide found significant differences in the way in which prenatal counseling is conducted, particularly between North American and European centers[24].

ISUOG has compiled the following Consensus Statement, which will be updated on a regular basis to take into account new studies in this field.

- Considering the emerging literature[1–3], we believe that, for the fetus with CHD, array comparative genomic hybridization (CGH) is much more appropriate than conventional karyotyping for ruling out or confirming genetic conditions that are potentially responsible for NDD in fetuses with CHD.
- Fetuses/neonates with hypoplastic left heart (HLH) and other lesions resulting in a postnatal univentricular circulation show an increased risk (> 40% in some studies[14,18–21]) of both brain morphometric abnormalities – evident on prenatal MRI and ultrasound – and NDD, independent of surgery. During prenatal counseling for these types of cardiac lesions, we recommend mentioning that there is an increased risk of NDD. A separate statement (see below) will address the issue of how to describe the risk.
- For all other CHDs, including TGA, it is felt that current evidence should be supported by further studies of children with prenatal diagnosis and optimal perinatal management before providing the same type of counseling as for those with a univentricular circulation.
- Very preliminary data show that brain morphometric abnormalities associated with NDD in the neonate can be diagnosed in the fetus[15]. However, further evidence from imaging and metabolic studies, including ultrasound and MRI or MRS, are needed prior to including detailed brain imaging in the routine prenatal surveillance protocol of fetuses with CHD. Currently,

prenatal brain imaging is recommended only to detect associated malformations or as part of investigational clinical trials.

- A balanced approach to the discussion of an association between NDD and CHD is essential in order to be relevant to the many cultural, religious and legal differences in different countries. Our society suggests that the following statement may be helpful during counseling: '... the majority of fetuses/neonates with isolated CHD do well. However, there is evidence that some have a degree of NDD, which cannot be predicted antenatally. The severity of this impairment varies from individual to individual, and the likely incidence varies with the type of CHD, being highest (up to 40–45% in some studies) in lesions with univentricular heart hemodynamics such as HLH. We advise genetic investigations, including array-CGH to rule out associated and syndromic forms of CHD.'
- The recommendation that fetuses with a prenatal diagnosis of major CHD should be delivered in a tertiary referral center, in which multidisciplinary neonatal management is available, is reinforced on the basis of the data discussed above.
- The recommendation regarding if and when to perform postnatal ultrasound, MRI/MRS and neurodevelopmental assessment is beyond the scope of this consensus statement. We recommend that national guidelines are followed to ensure appropriate evaluation of children and adolescents with CHD.

Writing group

D. Paladini*, Z. Alfirevic†, J. S. Carvalho‡§, A. Khalil‡, G. Malinger¶, J. M. Martinez**, J. Rychik††, Y. Ville‡‡ and H. Gardiner§§, on behalf of the ISUOG Clinical Standards Committee.

**Fetal Medicine & Surgery Unit, Istituto G.Gaslini, Genoa, Italy; †Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK; ‡Fetal Medicine Unit, St George's Hospital and St George's University of London, London, UK; §Centre for Fetal Cardiology, Royal Brompton Hospital, London, UK; ¶OB-GYN Ultrasound Unit, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; **Fetal Medicine, Barcelona Center for Maternal Fetal and Neonatal Medicine, Hospital Clínic and Sant Joan de Déu, University of Barcelona, Barcelona, Spain; ††Fetal Heart Program, Children's Hospital of Philadelphia, Philadelphia, PA, USA; ‡‡Maternité, Hôpital Universitaire Necker-Enfants Malades, Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, Paris, France; §§The Fetal Center, University of Texas Health Science Center at Houston, Houston, TX, USA*

References

1. Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, Romano-Adesman A, Bjornson RD, Breitbart RE, Brown KK, Carriero NJ, Cheung YH, Deanfield J, DePalma S, Fakhro KA, Glessner J, Hakonarson H, Italia MJ, Kaltman JR, Kaski J, Kim R, Kline JK, Lee T, Leipzig J, Lopez A, Mane SM, Mitchell LE, Newburger JW, Parfenov M, Pe'er I, Porter G, Roberts AE, Sachidanandam R, Sanders SJ, Seiden HS, State MW, Subramanian S, Tikhonova IR, Wang W, Warburton D, White PS, Williams IA, Zhao H, Seidman JG, Brueckner M, Chung WK, Gelb BD, Goldmuntz E, Seidman CE, Lifton RP. De novo mutations in histone-modifying genes in congenital heart disease. *Nature* 2013; **498**: 220–223.
2. Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, DePalma SR, McKean D, Wakimoto H, Gorham J, Jin SC, Deanfield J, Giardini A, Porter GA Jr, Kim R, Bilguvar K, López-Giráldez F, Tikhonova I, Mane S, Romano-Adesman A, Qi H, Vardarajan B, Ma L, Daly M. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science* 2015; **350**: 1262–1266.
3. Jansen FA, Blumenfeld YJ, Fisher A, Cobben JM, Odibo AO, Borrell A, Haak MC. Array comparative genomic hybridization and fetal congenital heart defects: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015; **45**: 27–35.
4. Hövels-Gürich HH, Seghaye MC, Schnitker R, Wiesnera M, Huber W, Minkenbergc R, Kotlarek F, Messmer BJ, von Bernuth G. Long-term neurodevelopmental outcomes in school-aged children after neonatal arterial switch operation. *J Thorac Cardiovasc Surg* 2002; **124**: 448–458.
5. Bellinger DC, Wypij D, Rivkin MJ, DeMaso DR, Robertson RL Jr, Dunbar-Masterson C, Rappaport LA, Wernovsky G, Jonas RA, Newburger JW. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation* 2011; **124**: 1361–1369.
6. Mitchell ME, Ittenbach RF, Gaynor JW, Wernovsky G, Nicolson S, Spray TL. Intermediate outcomes after the Fontan procedure in the current era. *J Thorac Cardiovasc Surg* 2006; **131**: 172–180.
7. Shillingford A, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics* 2008; **121**: 759–767.
8. Gaynor JW, Wernovsky G, Jarvik GP, Bernbaum J, Gerdes M, Zackai E, Nord AS, Clancy RR, Nicolson SC, Spray TL. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. *J Thorac Cardiovasc Surg* 2007; **133**: 1344–1353, 1353.e1–3.
9. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005; **25**: 32–36.
10. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation* 2015; **131**: 1313–1323.
11. Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetzky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, Robertson RL Jr, Evans AC, Newburger JW, Limperopoulos C. Delayed cortical development in fetuses with complex congenital heart disease. *Cereb Cortex* 2012; **23**: 2932–2943.
12. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr, Guizard N, McGrath E, Geva J, Annese D, Dunbar-Masterson C, Trainor B, Laussen PC, du Plessis AJ. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation* 2010; **121**: 26–33.
13. Mlczoch E, Brugger P, Ulm B, Novak A, Frantal S, Prayer D, Salzer-Muhar U. Structural congenital brain disease in congenital heart disease: results from a fetal MRI program. *Eur J Paediatr Neurol* 2013; **17**: 153–160.
14. Donofrio MT, Duplessis AJ, Limperopoulos C. Impact of congenital heart disease on fetal brain development and injury. *Curr Opin Pediatr* 2011; **23**: 502–511.
15. Masoller N, Sanz-Cortés M, Crispi F, Gómez O, Bennasar M, Egaña-Ugrinovic G, Bargalló N, Martínez JM, Gratacós E. Mid-gestation brain Doppler and head biometry in fetuses with congenital heart disease predict abnormal brain development at birth. *Ultrasound Obstet Gynecol* 2016; **47**: 65–73.
16. Schellen C, Ernst S, Gruber GM, Mlczoch E, Weber M, Brugger PC, Ulm B, Langs G, Salzer-Muhar U, Prayer D, Kasprian G. Fetal MRI detects early alterations of brain development in tetralogy of Fallot. *Am J Obstet Gynecol* 2015; **213**: 392.
17. Khalil A, Bennet S, Thilaganathan B, Paladini D, Griffiths P, Carvalho JC. Prevalence of prenatal brain abnormalities in fetuses with congenital heart disease: a systematic review. *Ultrasound Obstet Gynecol* 2016; **48**: 296–307.
18. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, Zimmerman RA, Spray TL, Gaynor JW, Vossough A. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg* 2009; **137**: 529–536.
19. Shillingford AJ, Ittenbach RF, Marino BS, Rychik J, Clancy RR, Spray TL, Gaynor JW, Wernovsky G. Aortic morphometry and microcephaly in hypoplastic left heart syndrome. *Cardiol Young* 2007; **17**: 189–195.
20. Miller S, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, Vigneron DB. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med* 2007; **357**: 1928–1938.
21. Sarajuuri A, Joniken E, Mildh L, Tujulin AM, Mattila I, Valanne L, Lönnqvist T. Neurodevelopmental burden at age 5 years in patients with univentricular heart. *Pediatrics* 2012; **130**: e1636–1646.
22. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation* 2012; **126**: 1143–1172.
23. Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014; **43**: 14–24.
24. Paladini D, Alfirevic Z, Carvalho J, Khalil A, Malinger G, Martinez JM, Rychik J, Gardiner H. Prenatal counseling for neurodevelopmental delay in congenital heart disease: results of a worldwide survey of experts' attitudes advise caution. *Ultrasound Obstet Gynecol* 2016; **47**: 667–671.

