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**Current understanding of the association of *neurodevelopmental delay and Congenital Heart Disease: impact on* prenatal counselling**

**An ISUOG Consensus statement.**

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An association between congenital heart disease (CHD) and neurodevelopmental delay (NDD) has long been recognised but remains poorly understood and is almost certainly multifactorial (1-8). A number of abnormal Magnetic resonance imaging (MRI), spectroscopy (MRS) or sonographic findings, specifically abnormal or delayed sulcation, reduced brain biometry and volumes and abnormal brain biochemistry have been described in the fetus and neonate with some forms of CHD (9-17). This suggests genetic factors (3) and the prenatal environment play an important role in the determination of postnatal neurodevelopment function, in contrast to traditional concepts attributing adverse neurodevelopmental outcomes to postnatal events such as perinatal hypoxia and peri-surgical damage. Furthermore, some large cohort trials have demonstrated an increased risk of NDD mainly – but not only - in children and young adults with univentricular circulations and, to a lesser extent 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 AHA (22), the conclusions of which 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 treat, if possible, 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 only be gained in the setting of well-designed studies. Furthermore the full extent of clinically important NND cannot be determined during the first years of a child’s life thus these studies will also require adequate follow-up. The current deficiencies in 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 cases of isolated CHD, usually associated with low mortality and low long term morbidity, such as TGA. On the other hand, the evidence available to date would suggest it is no longer possible, or ethical, to ignore this risk during prenatal counselling (14, 17, 23).

A recent survey, conducted by an ISUOG Task Force to gauge the attitudes and perceptions of health professionals from leading referral units for CHD worldwide has shown significant differences in the way prenatal counselling is conducted, especially if North-American and European centers are compared (24).

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has compiled the following Consensus Statement, which will be updated on a regular basis.

* Considering the emerging literature (1-3), we believe that, for the fetus with CHD, array-CGH is much more appropriate than conventional karyotyping. In this way, it is possible to rule out or confirm genetic conditions possibly responsible for NDD in foetuses with CHD.
* Fetuses/neonates with HLH and other lesions resulting in a postnatal univentricular circulation show an increased risk (> 40% in some studies) of both brain morphometric abnormalities – evident on prenatal MRI and ultrasound – and NDD, independent of surgery. During prenatal counselling for these types of cardiac lesions, we recommend to mention 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 counselling 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 foetuses with CHD. Currently, prenatal brain imaging is recommended to detect associated malformations or, also, as part of investigational clinical trials.
* A balanced approach to the discussion of an association between NDD and CHD is essential to be relevant to the many differing cultural, religious and legal differences in different countries. Our society suggests one helpful statement may be:”*…the majority of foetuses/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 haemodynamics such as HLH. We advise genetic investigations, including microarray-CGH to rule out associated and syndromic forms of CHD.”*
* The recommendation that foetuses with a prenatal diagnosis of major CHD should deliver in a tertiary referral center where multidisciplinary neonatal management is available is reinforced on the basis of the data discussed above.
* The question of if and when to perform postnatal ultrasound, MR and neurodevelopmental assessment is beyond the scope of this consensus statement. We recommend national guidelines are followed to ensure appropriate evaluation of children and adolescents with CHD (22).

This document will be regularly updated to take account of possible new studies in this field.

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