**Referee Commentary**

Re: Head growth in fetuses with isolated congenital heart defects: lack of influence of aortic arch flow and ascending aorta oxygen saturation.

F. A. R. Jansen, E. W. van Zwet, M. E. B. Rijlaarsdam, E. Pajkrt, C. L. van Velzen, H. R. Zuurveen, A. Kragt, C. L. Bax, S.-A. B. Clur, J. M. M. van Lith, N. A. Blom and M. C. Haak *Ultrasound Obstet Gynecol* 2016; **48**: XXX–XXX.

Congenital heart disease (CHD) and long-term neurodevelopmental delay is currently one of the hottest topics in fetal cardiology, generating much interest among many specialists. A link between the two was first suggested some years ago, but its etiological basis seemed multifactorial. However, since shifting the focus of this link to fetal life, there is growing evidence that *in-utero* circulatory changes, caused by the heart defect itself, may be responsible for abnormal fetal brain development and perhaps long-term brain function. Accepting this causation is a tall order and caution is needed.

An intuitive, yet simplistic, concept is that smaller heads contain smaller brains and perhaps this may be the starting point for some of the neurodevelopmental abnormalities reported in children and adults with CHD. Reports of a smaller head size in fetuses and neonates with CHD have often been interpreted to mean possible neurodevelopmental abnormalities. As a pediatric cardiologist, it was refreshing to read in the paper by Jansen *et al.* that the ‘status quo’ can, and should, be questioned.

Jansen’s is a well-conducted retrospective study of a relatively large cohort of fetuses with isolated mixed type of CHD. Fetal head circumference (HC) in mid-gestation and HC growth pattern were examined and compared with those in a normal population. Cases of CHD were clustered according to perceived characteristics of aortic blood flow (normal, obstructed, reversed) and ascending aorta saturation (normal, low, mixed). Briefly, the study showed a statistically significant decrease in HC growth with advancing gestational age in all groups of CHD, resulting in reduced head size in the third trimester (and at birth). Interestingly this was irrespective of aortic flow or saturation. At 20 weeks’ gestation, however, HC in CHD fetuses was not statistically different from that of the normal population, with the exception of those with tetralogy of Fallot. This is at variance with findings of other studies.

The questions remain: do statistically significant smaller heads at birth matter if absolute measurements fall within the normal range and is a slightly smaller HC clinically significant? Statistically smaller HC should not necessarily equate to abnormal brain development. Naturally, there are inherent limitations to any retrospective study. Two methodological strengths should, however, be highlighted. The first one relates to the likely certainty that CHDs were actually ‘isolated’. Absence of other ultrasound abnormalities at the 20-week scan and normal fetal karyotype offer no such guarantee but, in this study, which had a 70% live-birth rate, minimum follow-up time was 1 year, thus reducing the likelihood of including syndromic CHD. Second, the growth charts used as the standard reference were derived from a similar Dutch population that was evaluated over a similar timeframe as that of the CHD cohort. However, the lack of long-term neurodevelopmental follow-up prevents firm conclusions from being drawn about clinical significance of the findings. This of course calls for larger, prospective controlled trials. But will these ever be possible? It is therefore important that we continue to explore retrospective data obtained and analyzed in a sound manner. I look forward to reviewing a follow-on paper by the same group, comparing HC in this cohort with that of a cohort with non-isolated CHD.

Lastly, interpreting results goes beyond their statistical significance. Whilst small differences may influence future research on mechanisms that lead to altered fetal growth in cases of CHD, the long-term implications for the individual fetus that is diagnosed antenatally with isolated CHD are far from clear.

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