Opinion

Prenatal ultrasound diagnosis of Down syndrome. After major malformations, soft markers, nuchal translucency and skeletal signs, a new vascular sign?

Introduction

In the last 30 years considerable advances have been made in ultrasound technology and fetal medicine and, in terms of Down syndrome detection, we have witnessed ultrasonography evolve from a simple vehicle to guide the needle in amniocentesis procedures in ‘older’ women, to a powerful imaging tool for screening fetuses for markers of Down syndrome in women of all ages. Down syndrome detection continues to be one of the main challenges of perinatal medicine, and its detection seems as complex as the seemingly infinite number of signs and markers that have been reported in pre- and postnatal series. In this issue of the journal, Prefumo et al. report on another possible marker, i.e. a thoracic vascular malformation.

Malformations and second-trimester ‘soft markers’

In the 1980s, when imaging depended on the first generation of high-resolution real-time ultrasound machines, the suspicion of trisomy 21 was raised when major anomalies – including polyhydramnios, double bubble, ‘hydrocephaly’ and large cardiac septal defects – were detected. Subsequent analysis of features of newborns with trisomy 21 and the extrapolation of these signs to fetal ultrasonography took the prenatal diagnosis of Down syndrome a step further. These so-called ‘soft markers’, considered as risk factors for Down syndrome and other aneuploidies, were systematically described, in what was called the ‘genetic sonogram’ by researchers such as B. Benacerraf, D. Nyberg and K. Nicolaides, amongst others. The list is long and includes: nuchal fold, short femur, mild hydronephrosis, mild ventriculomegaly, echogenic focus, echogenic bowel, midphalanx hypoplasia of the fifth digit, brachycephaly, wide pelvic angle, flat profile, macroglossia and hypoplastic or absent nasal bone. Initially the presence of some of these signs was considered as a straightforward indication to offer an invasive procedure. Subsequently some were included in a scoring system and it is now generally agreed that they are most effectively applied in likelihood ratios to calculate the individual risk for a pregnant woman based on her own background risk of aneuploidy.

Nuchal translucency and first-trimester ultrasonography

Ultrasound assessment of early pregnancy became possible with the advent of transvaginal probes and the subsequent increased resolution of high-frequency transabdominal transducers. First-trimester ultrasonography was first proposed by experts demonstrating the feasibility of diagnosing severe malformations. The possibility of performing invasive procedures safely from 11 weeks’ gestation onwards by means of transabdominal chorionic villus sampling was the most important step towards a screening policy in the late first trimester. The observation that fetuses with Down syndrome and other aneuploidies have an accumulation of fluid in the neck region provided the basis of a systematic standardized measurement that is used as a screening tool in the first trimester. Nicolaides and The Fetal Medicine Foundation proposed measuring nuchal translucency (NT) thickness in order to calculate the individual risk for trisomy 21, 18 and 13 in the form of a likelihood ratio. The observation that increased NT is also associated with other anomalies (such as cardiac abnormality) and the routine application of image magnification, transformed this examination from one that merely measured NT to screen for aneuploidies into a comprehensive ultrasound examination for early detectable malformations.

Skeletal signs

Children with Down syndrome are known to have numerous musculoskeletal anomalies. Short femur and humerus, clino- and brachydactyly, brachycephaly and wide pelvic angle have been commonly searched for during the genetic sonogram. In recent years, however, additional skeletal findings such as hypoplastic or absent nasal bone and hypoplastic maxilla have been examined and reported in this journal and elsewhere. Other known skeletal anomalies in children with Down syndrome include, amongst others, the occurrence of 11 pairs of ribs (occurring in 33% of children with Down syndrome compared to 5% of the normal population), an abnormal upper cervical spine, and a hypersegmented sternum. Recently we showed that three-dimensional (3D) ultrasonography with the maximum mode improved visualization of the presence or absence of the nasal bones in fetuses with trisomy 21, and it can be expected that advances in this new technology will lead to a better demonstration of the skeleton in fetuses with suspected malformations.
New vascular signs

The most common abnormalities in children with Down syndrome are cardiac anomalies, which are found in around 50% of cases, atrioventricular septal defects accounting for half of these\textsuperscript{13}. The role and prevalence of other associated vascular abnormalities are likely to have been underestimated for years. In the child or adult with Down syndrome vascular anomalies are demonstrated when either they cause hemodynamic impairment or they are detected accidentally on diagnostic angiography performed prior to cardiac surgery. Vascular anomalies identified postnatally in Down syndrome individuals have often been reported in single cases or small series and have included: intrahepatic venous anomalies\textsuperscript{11,12}; pelvic vascular malformations\textsuperscript{13}; pulmonary vein obstruction\textsuperscript{14}; aorto-pulmonary collateral arteries\textsuperscript{15}; and anomalous aortic arch arteries as the aberrant course of the right subclavian or the vertebral artery\textsuperscript{16,17}.

In the fetus, however, the routine use of color Doppler ultrasonography enables the detection of vascular lesions not seen on gray-scale imaging. Since the beginning of the 1990s we have used routinely and encouraged others to use color Doppler ultrasound scanning as a part of the fetal examination\textsuperscript{18}. This approach has allowed us to detect a number of anomalies on routine ultrasonography that are not always suspected on gray-scale imaging, such as ventriculocoronary fistulae in second- and first-trimester fetuses\textsuperscript{19–22}, intracerebral\textsuperscript{23–25}, intrathoracic\textsuperscript{26}, or intrahepatic vascular lesions\textsuperscript{27}, and aberrant left subclavian and right subclavian arteries\textsuperscript{28,29}.

Interest in the vascular system in the fetus with Down syndrome was raised when it was discovered that Doppler interrogation of the ductus venosus (DV) in fetuses referred for NT screening could increase the detection rate. Matias et al. showed that 90% of fetuses with trisomy 21 exhibited reversal of flow in the DV, whereas only 3% of fetuses with normal chromosomes demonstrated this hemodynamic anomaly\textsuperscript{30}. Reversed flow in the DV is considered to have a likelihood ratio of 15 in increasing the risk for trisomy 21 in the recently developed concept of risk-oriented screening at 11–14 weeks’ gestation\textsuperscript{31}.

The routine investigation of the DV waveform prompted many examiners to apply color Doppler imaging in ultrasound screening. In Down syndrome fetuses we have reported in recent years two observations involving the vascular system:

1. Routine visualization of the ductus venosus with color Doppler ultrasonography enabled us to report on intrahepatic arteriovenous fistulae between the hepatic arteries and the umbilical vein in two fetuses with Down syndrome, one at 13 weeks’ and the other at 35 weeks’ gestation\textsuperscript{27}. This observation of the association between hepatic vascular malformation and Down syndrome has been demonstrated by others, who emphasized that in Down syndrome vascular anomalies of the umbilico-portal system could be the most common vascular defect\textsuperscript{11,12}. It is assumed furthermore that, in Down syndrome individuals, dysfunction of angiogenesis could play a role in the induction of the Down syndrome-associated features\textsuperscript{11}. Recent findings of placental hypovascularity of Down syndrome fetuses is further evidence of this hypothesis\textsuperscript{29}.

2. The second and most promising observation we have made recently was the common presence of an aberrant right subclavian artery (ARSA) in Down syndrome fetuses\textsuperscript{29}. This aberrancy describes the abnormal origin of the right subclavian artery not from the brachiocephalic trunk but as a separate vessel directly from the distal part of the aortic arch. It courses behind the trachea and esophagus to the right arm. An ARSA is the most common anomaly of the aortic arch and occurs in 0.5–1% of the general population, as reported from large autopsy and catheterization studies in adults\textsuperscript{3,16,33,34}. It is apparently a common finding in individuals with Down syndrome, occurring in 20–40% of them. Rathore and Sreenivasan\textsuperscript{16} reviewed in a case-control study the angiograms of patients with and without Down syndrome and found a higher rate of an aberrant right subclavian artery in the Down syndrome patients (36%) and abnormal origin of the left vertebral artery compared to non-Down syndrome individuals with cardiac defects. We performed a systematic analysis of 14 fetuses with Down syndrome and found this aberrant vessel in five of them (36%)\textsuperscript{29}. Our preliminary results suggest a likelihood ratio of this sign of 25 × the background risk.

The intrathoracic vascular lesion reported by Prefumo and coworkers\textsuperscript{1} in this issue of the journal can be considered as the fourth vascular abnormality reported in fetuses with trisomy 21. This entity is not known from postnatal series of individuals with trisomy 21. The authors found the lesion in the posterolateral region near the spine. The possibility of an artifact produced by reflection from adjacent bone is unlikely for several reasons: (1) the lesions were documented with at least two different machines; (2) the finding was reproducible despite visualization with a different angle of insonation; and (3) it was confirmed by means of pulsed (spectral) Doppler ultrasonography. Unfortunately no figure was added in the article to illustrate whether, on pulsed Doppler, the flow was continuous or pulsatile and in which range the peak velocities were registered. Histological analysis in one of the seven cases after termination confirmed that it was a hemangioma. If lesions are found in the liver, heart and brachiocephalic vessels of fetuses with Down syndrome, it is likely that the intrathoracic vasculature can be involved as well. Intrathoracic anomalies involving the bronchopulmonary system (abnormal bronchus, tracheomalacia etc.) are also known to occur in patients with Down syndrome\textsuperscript{34–36}.

There are aspects in this case series that are, in my opinion, of particular interest and worthy of emphasis:

1) The lesions were mainly seen in fetuses with a substantially increased NT, possibly associated in the
subgroup with trisomy 21 with spontaneous in utero demise, similar to both cases we have reported with hepatic lesions. This could explain why such observations have not been reported in postnatal series, and we have to assume that some vascular anomalies lead to hemodynamic impairment and subsequent death.

2) Resolution occurred in the two cases with normal chromosomes and these had a normal follow-up. It is known that one of the major features of chromosomally abnormal fetuses, especially those with Down syndrome, is delayed maturation. It is possible that apparently abnormal vascular signs are part of normal development resolving spontaneously, and in some situations they are still present until the late first trimester before resolving as well. During embryological development there are, for instance, connections between the descending aorta and the bronchial arteries, which resolve as soon as the pulmonary arteries develop. In fetuses with pulmonary atresia and underdeveloped pulmonary arteries these aortopulmonary collateral arteries persist (so-called major aortic-pulmonary collateral arteries (MAPCA)). Interestingly Holzer et al. reported recently on a child with Down syndrome and persistence of these aortopulmonary collateral arteries. A recent experiment on fetal lambs showed that even in normal fetuses there is persistent pulmonary arteriovenous shunting until the early neonatal period. All these data underline the possibility of a normal variant and developmental delay of the intrathoracic vasculature in the fetus. The question remains, however, whether some of these collateral arteries, arteriovenous fistulae or even hemangiomas are more common in individuals with trisomy 21 compared to normal fetuses. Furthermore, whether the intrathoracic vascular tree and its associated hemodynamic changes are related to increased fluid accumulation in the nuchal region in these fetuses has also to be ascertained.

3) There was a close relationship to the spine that was confirmed on histological analysis. In individuals with Down syndrome the spine is occasionally associated with developmental lesions and, when present, these could involve the neighboring vessels. In addition to the frequent findings of 11 ribs and anomalies of the vertebral bodies, especially in the cervical region, the spine of Down syndrome individuals may be a target for future investigations.

The case series in this issue of the journal and other associated observations documented in recent years emphasize that vascular lesions in individuals with trisomy 21 seem to be more common than expected and I think further investigation will elucidate their pattern and frequency. Research continues into the molecular basis of these vascular abnormalities. It is known that one of the major features of chromosomally abnormal fetuses, especially those with Down syndrome, is delayed maturation. It is possible that apparently abnormal vascular signs are part of normal development resolving spontaneously, and in some situations they are still present until the late first trimester before resolving as well. During embryological development there are, for instance, connections between the descending aorta and the bronchial arteries, which resolve as soon as the pulmonary arteries develop. In fetuses with pulmonary atresia and underdeveloped pulmonary arteries these aortopulmonary collateral arteries persist (so-called major aortic-pulmonary collateral arteries (MAPCA)).

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Prefumo et al. have made an interesting observation and the next step should be to find out how common such a vascular lesion is in normal fetuses in comparison to those with trisomy 21, and whether there are other vascular abnormalities.

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REFERENCES


