PRENATAL DIAGNOSIS OF HOLT-ORAM SYNDROME

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Abstract

Holt-Oram syndrome is a rare genetic syndrome, characterized by upper limb anomalies and congenital heart defects. The overall prenatal detection rate is low. We report a case of fetus with Holt-Oram syndrome with the current review of the literature.

Key words: *Holt-Oram syndrome, fetal echocardiography, enlargement of the right atrium, prenatal diagnosis*

INTRODUCTION

Holt-Oram syndrome is a rare genetic syndrome characterized by skeletal abnormalities of the upper limbs and heart defects and other cardiac disturbances especially cardiac conduction disease and a ventricular septal defect. It is inherited in an autosomal dominant pattern, characterized by high penetrance and variable expression. The overall prenatal detection rate is low, at about 39%

We report a case of fetus with Holt-Oram syndrome with the current review of the literature.

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CASE

A 32-year-old woman, gravida 2, para 2, was evaluated at our unit at 20 weeks of gestation. The family history was remarkable, father of the fetus had features of Holt-Oram syndrome, upper limb deformities, cardiac conduction disease and the mutation in the TBX5 gene. His brother died in the neonatal period due to congenital heart disease. Also the first child had upper limb deformity and heart defect: ventricular septal defect and mitral regurgitation. The child died at the age of eight months as a result of complications after cardiac surgery

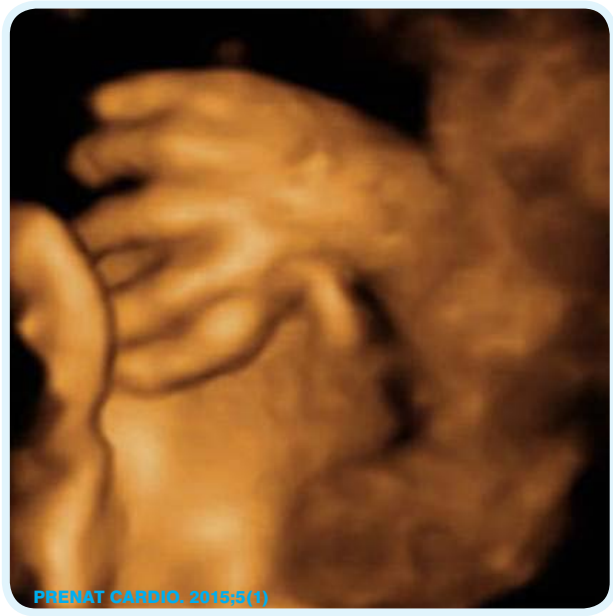

Photo 1. Upper limb deformity - abnormal structure and position of the thumb

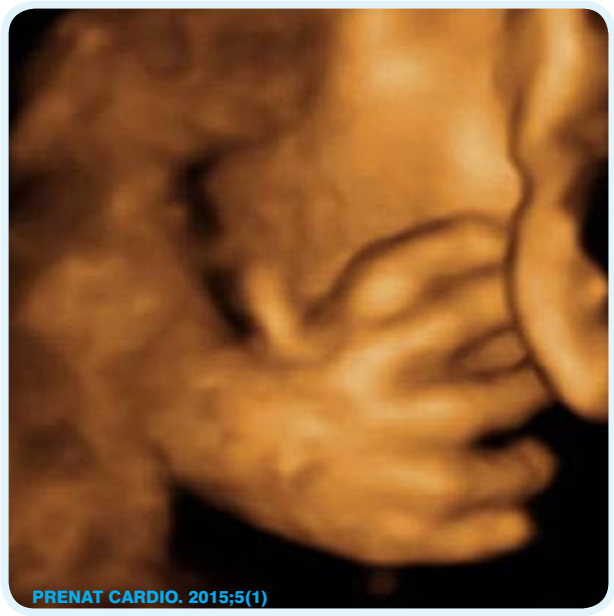

Photo 2. Upper limb deformity - abnormal structure and position of the thumb

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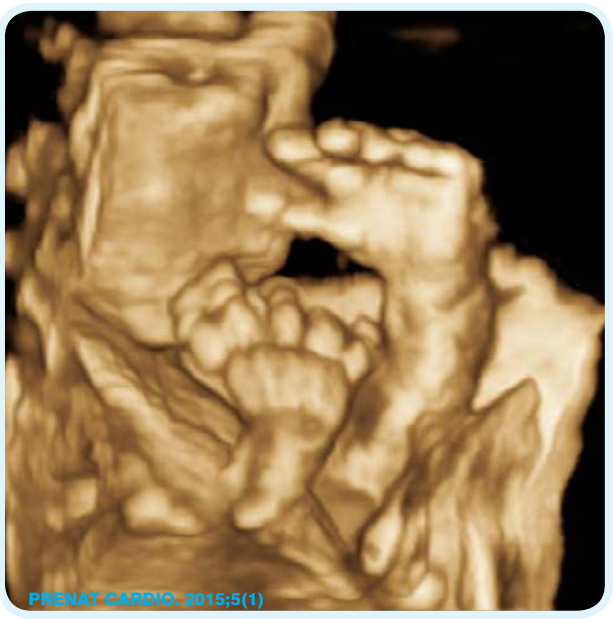

Photo 3. Upper limb deformity - abnormal structure and position of the thumb

In the current pregnancy diagnostic amniocentesis was performed because of family history and known mutations in the TBX5 gene. Molecular study revealed the presence of pathogenic mutation.

Ultrasound examination at 21 weeks of gestation revealed upper limb deformities (Photo 1, 2, 3), multiple ventricular septum defects (Photo 4, 5, 6) and tendency to bradycardia with prolonging atrioventricular conduction to 150 milliseconds (Photo 7, 8). The four chamber view was unusual because of an enlargement of the right atrium without a known cause, such as eg. tricuspid regurgitation (Photo 9). Pregnancy was monitored by the echocardiography up to 36 weeks. At 39 weeks' of gestation cesarean section was performed. The presence of bone malformations of both hands and congenital heart defect in the form of multiple defects in the ventricular septum were confirmed in newborn.

DISCUSSION

The Holt-Oram syndrome is a rare genetic syndrome, characterized by upper limb anomalies and congenital heart defects. Prenatal diagnosis of the Holt-Oram syndrome is mostly reported in familial cases when a more detailed ultrasound examination is performed, rather than by prenatal screening[1,2,3]. The overall prenatal detection rate is low, at about 39% [1].

We present a familial case with typical features of Holt-Oram syndrome. The skeletal abnormalities were observed in both hands. In the echocadriography we recorded multiple ventricular septal defects, right atrial enlargement and tendency to bradycardia with prolonging atrioventricular conduction to 150 milliseconds.

In the Holt-Oram syndrome upper-limb malformations range from triphalangeal or absent thumb to phocomelia. An abnormal carpal bones is present in all affected individuals. Skeletal abnormalities are usually bilateral and asymmetric, with left side often more affected than the right side[4]. Sunagawa at al. described an important role of 3-D ultrasound in prenatal diagnosis of Holt-Oram syndrome, which is very useful in visualization of skeletal abnormalities[5]. Similar observation had Sepulveda et.al, they found 3D examination to be extremely useful in the differential diagnosis of genetic

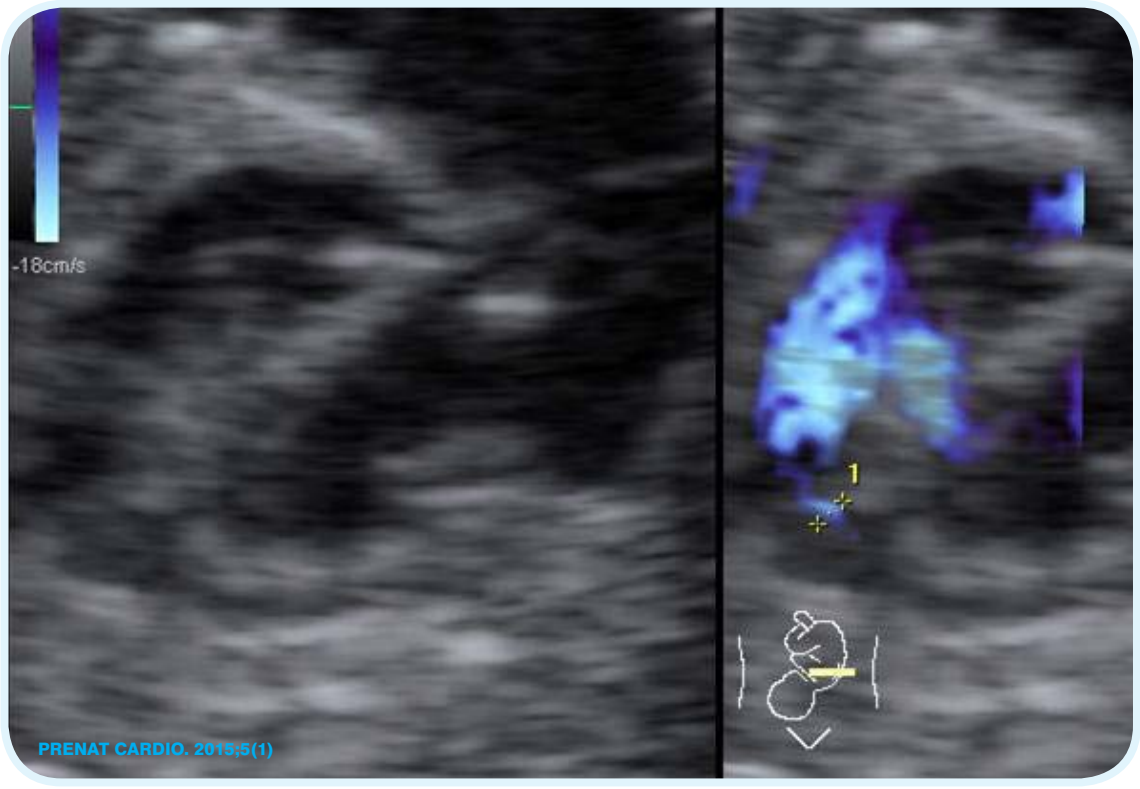

Photo 4. Multiple ventricular septum defects.

conditions involving the fetal limbs[6].

About 75 percent of individuals with the Holt-Oram syndrome have heart defects and other cardiac disturbances.[1,4]. A variety of structural heart anomalies are seen, with ASD and VSD being the most common. It is worth noting the observation of bradycardia with prolonging atrioventricular conduction.

This association with the Holt-Oram syndrome has not been previously described in fetal literature. Also right atrial enlargement is a new observation, described for the first time by Paladini et al. In 2014[7]. They reported two cases of ultrasound diagnosis of the Holt-Oram syndrome, both were characterized by significant right atrial enlargement. The similar feature was observed in our case. The right atrium was enlarged, without tricuspid regurgitation.

Prolonging atrioventricular conduction and right atrial enlargement can be the diagnostic keys in differential diagnosis in case of fetus with skeletal malformation of upper limb.

Photo 5. Multiple ventricular septum defects.

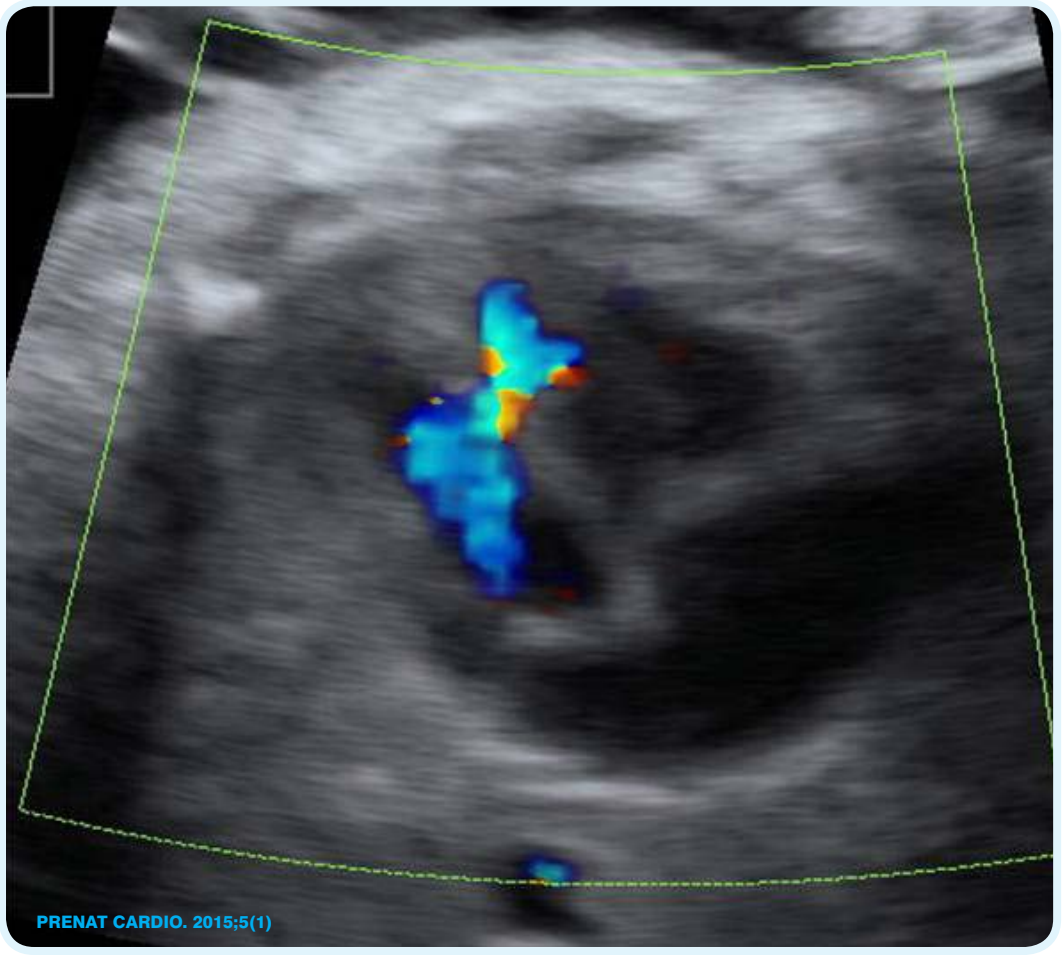

Photo 6. Multiple ventricular septum defects.

CONCLUSIONS

Holt-Oram syndrome can be diagnosed in prenatal period. Detailed fetal echocardiography can reveal subtle features such as prolonging atrioventricular conduction and right atrial enlargement which can be diagnostic tip in differential diagnosis.

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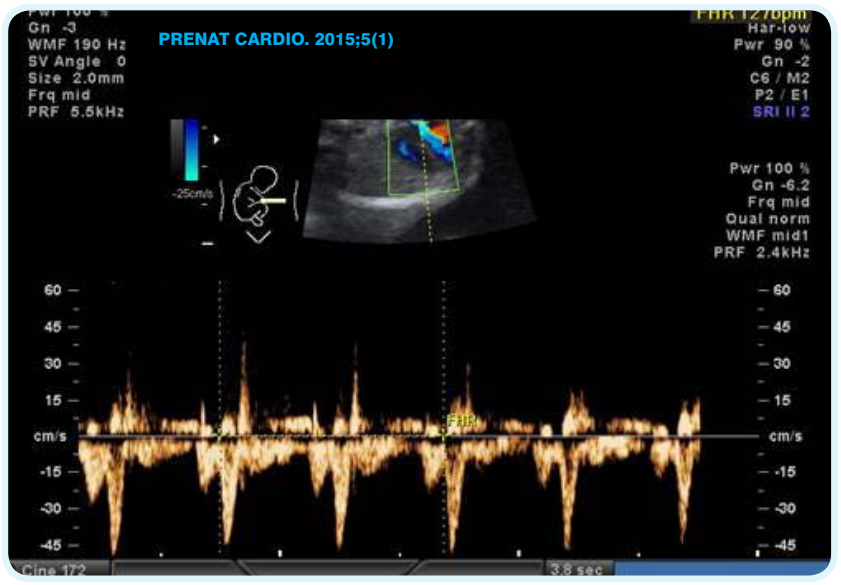

Photo 7. Fetal bradycardia.

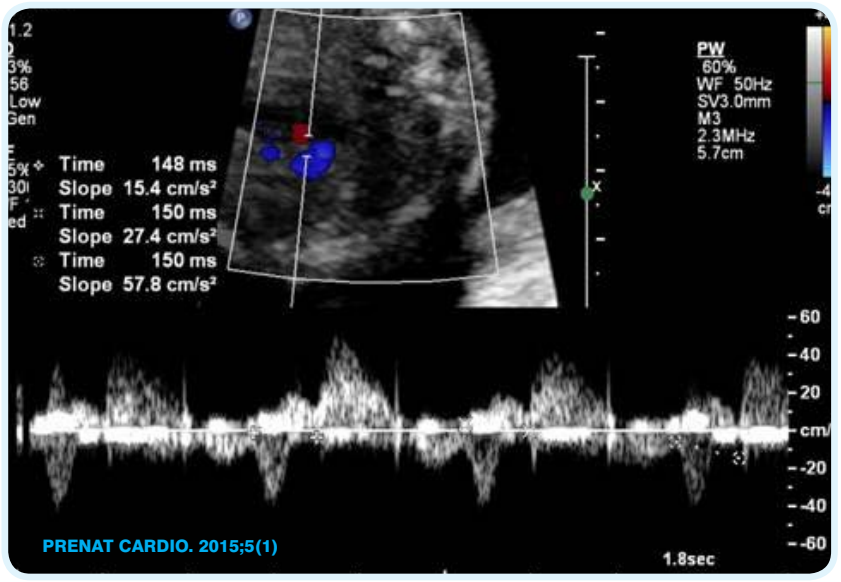

Photo 8. Prolonged atrioventricular conduction.

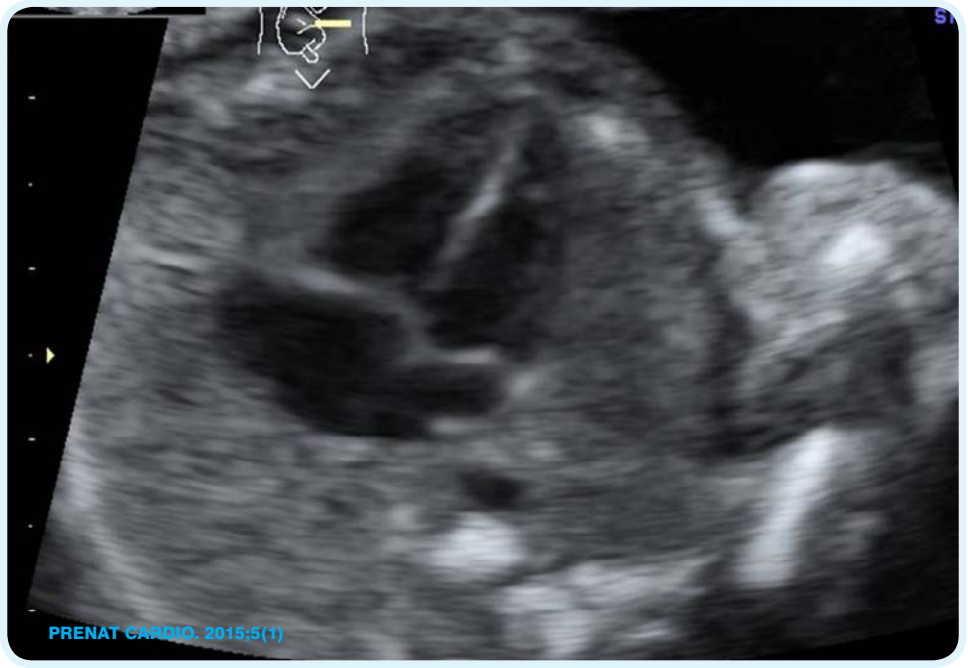

Photo 9. Enlargement of the right atrium.

Contribution of the authors in this research:

Hanna Moczulska: first draft of the manuscript, discussion, literature search, submition for publication

Maria Respondek-Liberska: photography for publication, discussion, final version of the manuscript

Conflict of interest: The authors declare no conflict of interest

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