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First-Trimester Placental Morphogenesis as Potential Marker for Early Diagnosis of Chromosomal Abnormalities

(Placenta As Marker of Chromosomal Abnormalities)

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***Abstract*— Multiple pathologies of the placenta can be identified during the first trimester of pregnancy thanks to the ultrasound diagnostics, and many molecular trophoblasts defects associated with it are still poorly understood. In other words, the 3D- and 4D-ultrasound are still the golden tool in early detection of abnormal fetal development. Using placenta as a marker in diagnosis of chromosomal abnormalities has detection sensitivity of only 3%, and is not syndrome specific, as in the case of Wolf-Hirschhorn syndrome where only few cases of hypotrophic placenta were reported. We describe the case of first-trimester pregnancy with diagnosis of pathologic placental morphology and intrauterine growth restriction of the fetus, with prenatal genetic screening testing which confirmed existence of Wolf-Hirschhorn syndrome. Suspicion for chromosomal abnormalities was raised due to placenta ultrasound examination only and this case report outlines the clinical significance of the placenta as a novel marker for Wolf-Hirschhorn syndrome, since other clinical indications in this case were not present.**

Keywords*— *Placenta, Wolf-Hirschhorn Syndrome, 3D- and 4D-ultrasound.

I. BACKGROUND

During fetal development the human placenta undergoes physiological remodeling of the spiral arteries with deep placentation as part of the normal fetal development which can be negatively impaired in case of some pathology.[1] It was reported that a number of characteristic histological lesions of placenta can be associated with some pathologies such as pre-eclamsia and intrauterine growth restriction (IUGR).[2] Some reports described presence of hypotrophic placenta in second trimester old babies who were delivered as the pregnancy was terminated, but without any significan macroscopic or histological abnormalities.[3] Some studies also shown that increased thickness of the placenta (above 90%) leads to increased fetal mortality.[4] Wolf-Hirschhorn syndrome (WHS) is a genetic disorder associated with a partial deletion of the short arm of chromosome 4 (4p16.3) and with wide spectrum of clinical manifestations, such as facial abnormalities, congenital heart defects, skeletal anomalies, poorly formed ears and microcephaly. The WHS is also characterized by pre- and postnatal growth delay and a broad nasal tip malformation known as a „Greek warrior helmet appearance".[5,6,7] The WHS is not common for the Balkan region and only sixs cases were reported from Bosnia and Herzegovina so far.[8,9] Here we present the case of early WHS discovery based on placenta's ultrasound examination and its morphological changes only, since the other fetal measurements were in the normal range.

II. CASE DESCRIPTION

A 20-year-old healthy female in 13 weeks+2 days of spontaneous pregnancy, with no history of positive family anamnesis of any genetic pathologies, was screened for the first trimester ultrasound. The patient had one miscarriage in the 11th week in age of 19. Ultrasound examination was performed with ultrasound machine Voluson E6 and findings included: alive fetus, visualized fetal heart activity, fetal heart rate 163 bpm, crown-rump length (CRL) 70.6 mm, nuchal translucency (NT) 2.2 mm (Fig. 3A), biparietal diameter (BPD) 19.8 mm, ductus venosus PI 1.530 (Fig. 3B), placenta circular, amniotic fluid normal, 3 vessels cord. For

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chromosomal markers: nasal bone present, tricuspid doppler normal. Examination of fetal anatomy revealed normal skull/brain and spine appearance. Also the fetal heart and abdominal wall appeared to be normal. During ultrasound examination stomach, bladder, kidneys, hands and feet were all visible and appeared normal. However, the placenta examination showed placenta thickness of 31.6 mm circularly present on all uterine walls and fully occluding the uterine mouth, 11 mm thick on the front wall and 31.6 mm on the back and fundus, indicating diagnosis of pathologic placental morphology (Fig. 1). Geometrically, in ultrasound examination, the fetus was smaller for one week than expected at this stage of gestation when calculating from the absence of menstruation.

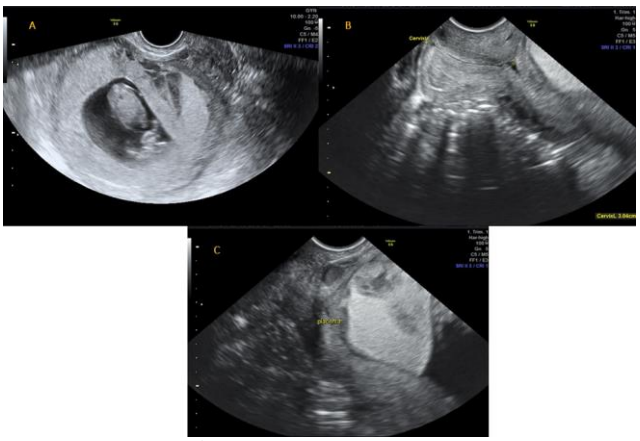

Fig. 1: 2D ultrasound fetal screening presenting pathologic placental morphology. A: inhomogenous placenta. B: T-shaped cervikal canal. C: the placenta covers the inner uterine mouth.

The background risk for aneuploidies was calculated based on maternal age (20 years). All biophysical markers were corrected as necessary according to several maternal characteristics including racial origin, weight, height, smoking, method of conception and parity. The estimated risk was calculated by the FMF-2012 software (version 2.8) and was based on findings from extensive research coordinated by the Fetal Medicine Foundation (UK Registered charity 1037116). The Background/Adjusted risk for Trisomy 21 of 1:1109/1:3056, Trisomy 18 of 1:2793/1:8465 and for Trisomy 13 1:8739/<1:20000, indicated a low aneuploidies risk (Fig. 2). The risk for spontaneous delivery before 34 weeks was 1:2897. TORCH test of the patient was negative, and possible viral infections could be excluded.

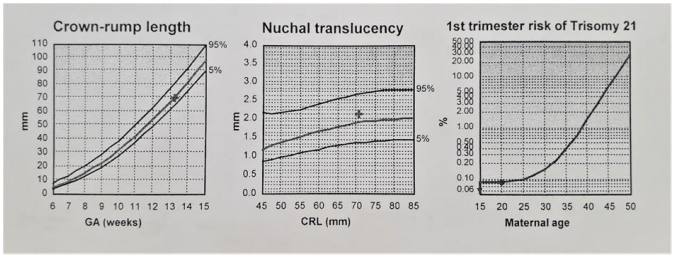

Fig. 2: First-trimester screening report for aneuploidies risk.

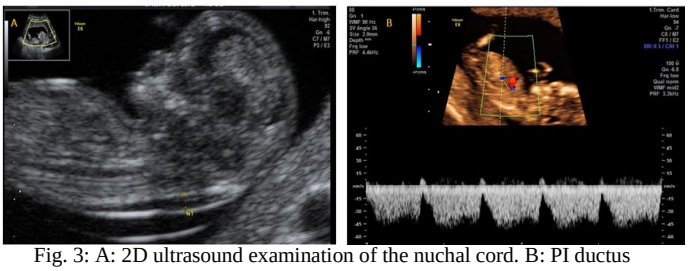

Fig. 3: A: 2D ultrasound examination of the nuchal cord. B: PI ductus venosus.

Guided by morphological changes of the placenta, its ultrasound imaging, localization and volume, and inhomogeneous appearance, as the only indicators of pathological status, the gynecologist in charge raised suspicion of chromosomal aberration and based on medical history of sponatneous abbortion, recommended additional non-invasive prenatal genetic testing. Based on the fetal ultrasound examination only, the Wolf-Hirschhorn syndrome could not be diagnosed. „MyPrenatal Test“, a prenatal genetic screening test, was positive for microdeletion in 4p16.3 chromosomal region, confirming diagnosis of Wolf-Hirschhorn syndrome. The patient was referred with findings to the clinical center ethics committee, and its members recommended early amniocentesis, without suggestions for the additional FISH analysis. Results of early amniocentesis showed a normal XY karyotype, but further FISH analysis was not performed. The ethics committee suggested termination of pregnancy, and after genetic counseling, the parents decided to do so. This is the first report in Bosnia and Herzegovina where diagnosis of Wolf-Hirschhorn syndrome could be made based on the ultrasound examination of fetal placenta only, and which was also confirmed with non-invasive prenatal testing. The gynecologist developed suspicion on WHS based on placental morphology and history of spontanous abbortion only, since the other clinical parameters and patient history were not indication for the WHS genetic screening.

The pathohistological analysis of placenta showed the following: placenta with ruptured placental tissue measuring 110x110x30 mm, with separately received fragments of placental tissue measuring 60x50 mm. Fetal side of centrally positioned umbilicus 160 mm long, at the cross section with three distinctive vascular lumens, the amniotic membrane less transparent. Maternal side torn, partly made up of brown spongy mole tissue, partly extremely blood-permeated. Pathohistological diagnosis: inflammation of fetal amniotic membrane. Subchorionic thrombosis and local ischemic enclosure. Local edema and fibrotic changes on stromal villi. Local intervillous fibrin deposition. After termination of the pregnancy, both parents did karyotype testing which turned out to be normal. A six months after abortion the patient concived spontanously again and healthy child was born.

III. DISCUSSION

The role of ultrasound in the diagnosis of fetal genetic syndromes serves as a screening tool for the recognition of fetal abnormalities. Thanks to the development of ultrasound diagnostics and using high-frequency transvaginal probe with strong resolution, the detection of abnormalities has been moved from the second to the early first trimester. A fetal ultrasound screening is non-invasive, high-risk fetuses are isolated in the low-risk group, and further genetic screening of

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non-invasive and invasive tests should be performed to confirm the diagnosis. In addition to knowing the patterns seen with individual syndromes, identifying these abnormalities may lead to recommendations for definitive diagnostic testing, preparation for the postnatal period, or both.

A placental changes in its structure, localization, insertion and thickness belong to ultrasonic markers with very low sensitivity for chromosomal aberrations.[10] Homogeneous thickening of the placenta can be idiopathic or caused by maternal diabetes mellitus, non-immune and immune hydrops, infections, aneuploidy (trisomy), fetal or maternal anemia, heterogeneous thickening, placental hemorrhage, multiple pregnancy, placental tumor, etc. It is reported that these occur in 0.6% of pregnancies. Enlarged thickness of placenta, even when isolated, has been associated with increased perinatal morbidity and mortality.[11]

Most perinatal deaths are associated with anomalies, non-immune hydrops, placental abruption, and premature rupture of membranes. Diagnostic ultrasound has been used in clinical obstetrics for almost half a century. However, it appears in the literature that less attention is paid to placental examination than to a fetus or a pregnant uterus. This is somewhat unexpected, given the obvious major functions that this organ performs throughout pregnancy. Placental examination plays a major role in the evaluation of normal and abnormal pregnancy. Methodological sonographic evaluation of the placenta should include: location, visual size assessment (and, if abnormal, thickness and / or volume measurement), implantation, morphology, anatomy, as well as anomaly search, such as additional lobes and tumors, age, abruption of placenta or congenital viral infection. The ultrasound appearance of thick, heterogeneous and small placenta may provide information on possible adverse outcomes in pregnancy. The size of the placenta is significant in assessing pregnancy problems such as preeclampsia, too.[12]

In this case report we present evidence of importance of placental morphogenesis as marker in early diagnosis of chromosomal abnormalities such as 4p-syndrome, also known as Wolf-Hirschhorn syndrome. That is a rare genetic disorder chracterized by birth defects, cranio-facial features in infancy, structural brain and skeletal abnormalities, urinary tract malformations and other serious medical problems. Specialized genetic testing such as FISH and microarray are required to confirm the presence of WHS. The size of gene deletion can be different in affected individuals, and larger deletion will result in more severe intellectual disability and physical abnormalities than smaller deletions. The method of detection of chromosomal deletion in region 4p16.3 is a flourescence in situ hybridisation (FISH) using Bacterial Artificial Chromosomes (BAC) probes which enable easier and faster cytogenetic analysis.[13] These test are performed on cells from chorionic villus sampling or amniocentesis during pregnancy, on samples of cord blood or peripheral blood after the birth, or on products of conception in case of miscarriage.

Early ultrasound examination is crucial not only for monitoring fetal development but also for early detection of genetic abnormalities, since even when fetal screening seems normal, the smallest changes in the placenta, as a novel potential marker, can serve to diagnose gene mutations, early during the first-trimester.

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