

CASE STUDY

PLACENTAL MOSAICISM: COMPLETE DISCORDANCE BETWEEN THE PLACENTA AND THE FETUS. CLINICAL CASE RECORD

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ABSTRACT

NIPT with the analysis of all chromosomes for aneuploidy screening. Chromosomal microarray 750K, routine karyotyping and Whole-exome sequencing and Sanger sequencing were used for the analysis of the clinical situation

Sonographic fetal abnormalities were accompanied by the placental mosaicism (trisomy 16), fetal partial uniparental disomy of the short arm of chromosome 16.

NIPT with the analysis of all chromosomes is a powerful tool to identify placental mosaicism, which in turn can manifest itself as nonspecific abnormalities in biochemical markers, placental dysfunction, growth retardation, fetal malformations, preterm birth, etc. If placental mosaicism is suspected, the optimal clinical strategy is to perform amniocentesis and placentocentesis simultaneously with a complete genetic examination of the obtained material

KEY WORDS: Placental mosaicism, congenital malformations, NIPT, karyotyping, chromosomal microarray analysis, pregnancy planning

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INTRODUCTION

Chromosomal mosaicism is the presence of two or more cell lines with different karyotypes in an organism developing from a single zygote. It can involve all tissues of the body (true fetal mosaicism) or be limited to only some of them (tissue-limited mosaicism). When the karyotype of the embryo itself is normal and chromosomal abnormalities are found only in the provisional tissues of the embryo (chorion, placenta), limited placental mosaicism is implied. Chromosomal abnormalities of the placenta can affect embryogenesis in different ways: from complete lack of influence to intrauterine growth retardation and fetal death, which depends on the type of chromosomal abnormality, involvement of extraembryonic tissues and quantitative ratio of normal and abnormal clones associated with epigenetic effects [1-3].

The most common phenomenon is the limited fetal mosaicism (Table I), with a rate of 87.3% among all pathologies. At the same time, the marker chromosomes are most often involved in mosaicism (31.6%); most rare are chromosome anomalies, excluding vital and sexual (2.8%) (Table II) [4].

It is known that Type III mosaicism has the most significant effects on the course and outcomes of pregnancy, resulting in "false-positive" nonspecific results of screening studies with individual risk calculation, reduced PAPP-A protein levels, placental dysfunction, premature birth, fetal growth retardation, stillborn pregnancy, fetal malformations and other adverse effects in pregnancy [5, 6].

Diagnosis of placental mosaicism is a complex practical and methodological problem that requires a clear

understanding of both the possibilities of each analytical method and the peculiarities of histogenesis at the early stages of embryonic development, as there is no universal method of diagnosis, including placental mosaicism (Fig. 1 [4]).

CASE REPORT

Patient K., 31 years old, 16th week of pregnancy, on her own initiative, presented at the Nadiya Clinic of Reproductive Medicine for non-invasive prenatal genetic DNA testing (NIPT) for chromosomal abnormalities of the fetus, NIPT Verify, Illumina (for all chromosomes).

The obtained result: trisomy of chromosome 16. Medical and genetic consultation is recommended.

History:

Suffered from primary infertility for 3 years.

Diagnosis: First pregnancy, primary infertility managed using ART (intrauterine insemination with controlled ovarian stimulation). Placenta previa.

Family history not compromised. Occupational hazards not determined. Exacerbation of HSV and acute pharyngitis at week 9, ARVI at week 13-14 (without serological diagnosis).

Screening tests in the first trimester of pregnancy: week 12+4 days: CRL 61.6 mm, nuchal translucency thickness 1.4 mm, beta-HCG 1.017 IU, PAPP-A 0.177 MoM, PIGF 0.329 MoM.

Individual estimated combined risk:

- Trisomy 21: 1/50;

Table I. Proportions of the types of mosaicism in its general structure (according to [4])

Mosaicism type	Group	Karyotype			Specific weight
		Trophoblast	Mesenchyme	Amniocytes	
I	CPM	Abnormal	Normal	Normal	34.8%
II	CPM	Normal	Abnormal	Normal	42.3%
III	CPM	Abnormal	Abnormal	Normal	10.2%
IV	TFM	Abnormal	Normal	Abnormal	1.6%
V	TFM	Normal	Abnormal	Abnormal	5.8%
VI	TFM	Abnormal	Abnormal	Abnormal	5.4%

CPM - Confined Placental Mosaicism

TFM - True Fetal Mosaicism

Table II. Proportions of mosaic anomalies in the general structure of mosaicism (according to [4])

Aberration	Specific weight
47,+mar	31.6%
Sex chromosome aneuploidies	26.00%
Frequent (vital) trisomies(13, 18, 21)	20.00%
Structural displacement	9.9%
Polyploidy	3.3%
Rare autosomal trisomies	2.8%

- Trisomy 18: 1/1022;
- Trisomy 13: 1/1220;
- Fetal growth retardation: 1/8.

The patient was informed that the result was more likely due to the tissue-limited placental mosaicism, there was a high risk of intrauterine growth retardation or fetal death.

Recommended:

- Ultrasound examination of the fetus;
- Invasive genetic diagnosis (placentocentesis and amniocentesis with karyotyping);
- Free verification of NIPT Verify results using the NIPT SAGE-Nadiya.

The results at week 18-19:

NIPT SAGE-Nadiya: trisomy 16 (z-score 13.75 (N -6... + 6))

Placentocentesis: 47,XX,+16.nuc ish(D16Z3x3) [50]. Female karyotype with regular trisomy of chromosome 16 (verified by FISH: 3 signals corresponding to chromosome 16, 100%).

Amniocentesis: 46,XX.nuc ish(D16Z3x2) [50]. Normal female karyotype. FISH verified (2 signals corresponding to chromosome 16, 100%).

Ultrasound:

- unilateral aplasia of the radial bone (HP:0011908)
- unilateral agenesis of the kidney (HP:0000122)
- fetal growth retardation (HP:0001511).

The pregnancy was terminated due to medical reasons.

Results of fetal fibroblast karyotyping: 46,XX.nuc ish(D16Z3x2) [50]. Normal female karyotype.

In order to exclude genetic factors of fetal pathology, as well as to address the strategy for pregnancy planning and calculation of a posteriori genetic risks, a sample of

fetal fibroblasts was sent for chromosomal microarray analysis (comparative genomic hybridization) and full exome sequencing.

Chromosomal microarray analysis showed a partial uniparental disomy of the short arm of chromosome 16: arr[hg19]16p13.3p13.11(4,781,662-15,965,258) x2 hmz (11.18 MB) (Fig. 2).

The region of uniparental disomy includes 103 OMIM genes, of which the phenomenon of haploinsufficiency leads to confirmed pathogenicity: 13, including ABAT, ALG1, CIITA, EMP2, ERCC4, GRIN2A, LITAF, MYH11, NDE1, PARN, PMM2, ROGDI and SET.

In addition, 2 microstructural syndromes of predisposition to neurocognitive disorders have been described for this region: 16p13.11 reversed microdeletion syndrome and 16p13.11 reversed microduplication syndrome. These syndromes are formed in the germ cells reciprocally, i.e., duplication in one will be accompanied by deletion in the other and vice versa, due to the presence of highly homologous repeated DNA fragments (LCR16's), and will be manifested in delayed psychocognitive development and certain birth defects. That is, the molecular structure of the 16p13 locus provides a basis for genetic instability and increased risks of clinically significant microstructural disorders.

Schulze et al. [7] confirm the presence of 16 loci with differential methylation in the chromosome, where map abnormalities result in the development of congenital genetic pathologies, as evidenced by cases of fetal growth retardation and/or congenital genetic conditions associated with partial uniparental disomy and abnormalities in the DNA methylation map of different loci of chromosome 16 in the normal karyotype of the fetus/child [8].

Whole exome sequencing.

The results showed a mutation in heterozygous status with unknown clinical significance, which is likely to have a clinical outcome in the form of the above clinical picture. Gene: NIPBL. Mutation: c.4332A>C (p.Arg1444Ser). The mutation is found in the gene associated with Cornelia de Lange syndrome, type 1 (autosomal dominant inheritance). Most cases of the disease are sporadic, occurring de novo. Cornelia de Lange syndrome, type 1 is characterized by severe prenatal hypoplasia, significant retardation in physical and intellectual development and significant malformations.

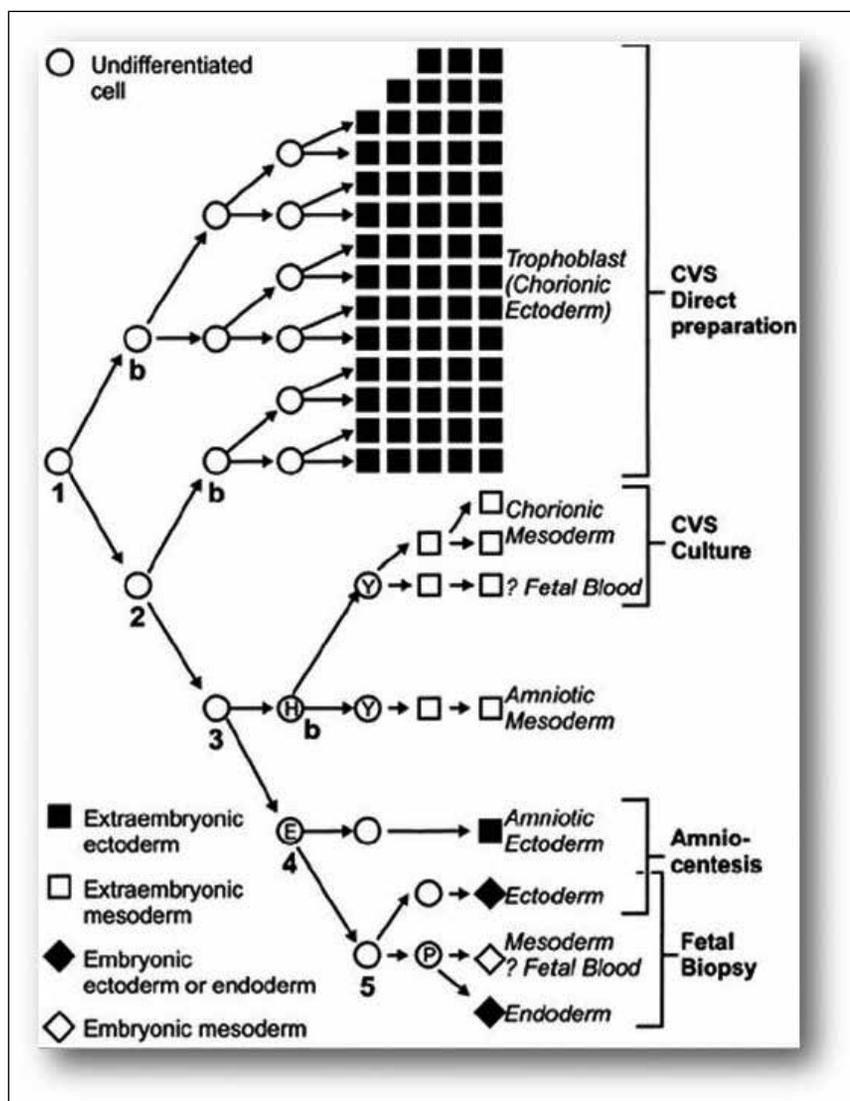


Fig. 1. Diagram of cell lines that differentiate at the early stages of embryonic development [4].

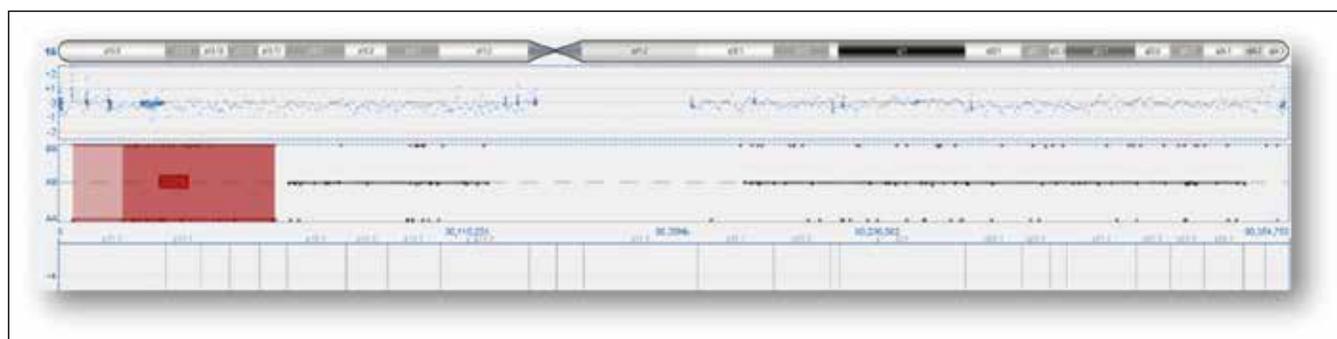


Fig. 2. Partial uniparental disomy of the short arm of chromosome 16 (bands 16p13.3-16p13.11)

Given that the clinical significance of the mutation has not been identified, genetic study of the parents is recommended for NIPBL mutation c.4332A>C to determine its causality.

Random findings of the whole exome sequencing included: heterozygous carrier of mutations of autosomal recessive pathologies:

- gene of spastic paraplegia, type 47 AP4B1, mutation c.1160_1161del (p.Thr387Argfs*30) (pathogenic);

- BTD biotinidase deficiency gene, mutation c.1336G>C (p.Asp446His) (pathogenic) and autosomal-dominant pathology

- Charcot-Marie-Tooth gene, type 2Q DHTKD1, mutation of the splicing site c.1897-1G>A (probably pathogenic).

Based on the above, the couple should be examined for a hidden carrier of recessive pathology (Carrier Screening) in order to minimize the risks of having a child with recessive genetic pathology.

Additional examination of the couple for the carrier of the NIPBL mutation c.4332A>C will probably clarify the origin of the described pathology. If a mutation is found in one of the genetic parents, it will allow the exclusion of the causative nature of the mutation and the conclusion that the mutation is nonpathogenic, and therefore the only factor of fetal malformations may be fragmentary uniparental disomy of the short arm of the chromosome 16. The latter probably occurred after meiotic chromosome nondisjunction in the gametogenesis of one of the parents with subsequent self-correction of the embryo, during which a cascade of chromosomal “breaking-assembly” (chromothripsis) occurred and a fragmentary uniparental disomy was formed. A priori recurrent genetic risk for the couple is low for uniparental disomy and increased for possible chromosomal abnormalities (total 8%, chromosome trisomy 16 - 2%). In this case, the couple is advised to perform pre-implantation genetic testing for further ART to exclude the transfer of the aneuploid embryo. Chromosomal microarray analysis is recommended at the stage of prenatal examination to exclude uniparental disomy.

If the mutation is not identified in the couple, this will give the grounds to recognize possible causality of the mutation. Most cases of Cornelia de Lange syndrome occur de novo. Given the possibility of gonadal mosaicism in the parents (germline mosaicism in the parents), the recurrence risk is 1.5%. There is still a recurrence risk for chromosomal abnormalities, as described above. In this case, it would be appropriate to include pre-implantation genetic testing of embryos for NIPBL mutation c.4332A>C in the diagnostic program.

The preconception genetic testing showed that the husband is a carrier of the NIPBL mutation c.4332A>C. No additional genetic risks were identified after the couple had been tested for hidden carrier of recessive pathology (Carrier Screening). The couple is planning a pregnancy using ART with pre-implantation genetic testing.

It should be noted that the described clinical case highlighted another urgent problem: improving the quality assurance system in obstetrics and gynecology, given its importance in the prevention of maternal and infant losses and in population health in general. It is known that financial availability of expert genetic testing for more than half of patients is significantly limited [9]. Under conditions of out-of-date regulations of medical genetics (Order No. 641/84 of the Ministry of Health of Ukraine of 31.12.2003), absence of unified clinical protocols, including expert methods of genetic testing, unavailability of clinical protocols from international sources (due to financial factors), it is impossible to unify approaches in patient management, ensure that patients have access to the necessary test methods and, as a result, to provide timely and high quality medical care. Therefore, organizational measures to improve the quality of obstetric and gynecological, as well as genetic services, aimed at preserving the life and health of a newborn and improving the quality of medical care for pregnant women and mothers, are extremely important. It is a necessary condition for ensuring the citizens' right to

health, successful development of the national health care system and improvement of the demographic situation in Ukraine.

CONCLUSIONS

NIPT with the analysis of all chromosomes is a powerful tool to identify placental mosaicism, which in turn can manifest itself as nonspecific abnormalities in biochemical markers, placental dysfunction, growth retardation, fetal malformations, preterm birth, etc. If placental mosaicism is suspected, the most optimal clinical strategy is to perform amniocentesis and placentocentesis simultaneously with a complete genetic examination of the obtained material. Close collaboration between geneticists and patients at the screening phase is the key to accurate genetic diagnosis and the development of a pregnancy planning program to minimize genetic risks. Organizational measures to improve the quality of obstetric and gynecological, as well as genetic services, aimed at preserving the life and health of a newborn and improving the quality of medical care for pregnant women and mothers, are extremely important.

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Conflict of interest:

The Authors declare no conflict of interest.

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