THE RARE REGULAR TRISOMY 17: FREQUENCY AND PHENOTYPIC PORTRAIT

Nickolay Veropotvelyan
Multiregional Centre of Medical Genetics and Prenatal Diagnostics
3A Vyzvolennya sq., Kryvyi Rih, Ukraine, 50000
veronick110@gmail.com

Abstract

This paper presents the data from our own research of frequency of full regular trisomy 17 (T17) based on 1808 samples of miscarriages, 1572 medical induced abortions at 5–11 weeks of gestation, and 9689 samples of invasive prenatal tests done between 11 and 24 weeks of pregnancy. The frequency of full T17 in all miscarriages was 1/152 and in medical induced abortions – 1/524; the population frequency of T17 in the first trimester accounted for 1/454.

Additionally, it presents the data on the proportion of T17 of all autosomal trisomies structure in different periods of fetal development. When performing invasive prenatal testing we detected 4 cases of T17 that represented 0,58 % of autosomal trisomies among fetuses of 11–22 gestational weeks.

Furthermore, the paper introduces a symptom-complex of fetal abnormalities that are typical of regular full trisomy 17.

Keywords: chromosomal abnormalities, trisomy 17, rare trisomies, miscarriages, ultrasound prenatal diagnostics.

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1. Introduction

Chromosomal abnormalities (CA), whose frequency makes up 50–60 % of early reproductive losses and due to the natural mortality rate goes down to 0.5–0.7 % of live births, holds a specific place in the structure of congenital and hereditary diseases.

Trisomies constitute the largest proportion of all chromosomal abnormalities.

Over the past 40 years, or even more, there have been performed only a few large-scale studies in which the number of karyotype sample from missed abortions exceeded 1,000 specimen of non-developing products of concept [1–4]. While these studies were carried out at different times in different countries and populations, in all of them trisomy prevailed in the structure of chromosomal abnormalities found in missed pregnancies, with its portion varying from 44 to 66 % (**Table 1**).

Table 1

The study of first trimester miscarriages karyotypes

	Boue 1975	**Hassold 1980**	**Kline 1987**	**Menasha 2005**
Total analyzed	1498	1000	2098	1203
Total anomalies	921 (61,5 %)	463 (46,3 %)	776 (37,6 %)	792 (65,8 %)
Trisomy	479 (52,0 %)	207 (44,5 %)	368 (47,4 %)	522 (65,9 %)

The analysis has shown unequal participation of different chromosomes in the structure of autosomal trisomies. Trisomies 21, 18 and 13 in newborn infants generally account for 95 % of chromosomal abnormalities. In the earlier stages of fetal development, this rate is lower. Therefore it is assumed that all trisomies, except 21, 18, and 13, are rare.

Rare trisomies should be a key focus, since phenotype of fetuses with such abnormalities is not yet described for their low frequency. Until now it has been believed that trisomy 1 and trisomy 19 are incompatible with postimplantation development [5].

Our research experience over the last 20 years proves that there is a whole spectrum of autosomal trisomies (including such rare ones as regular trisomies 1 and 19) in the structure of early reproductive losses of first trimester.

The analysis of frequency of rare trisomies detected in the process of prenatal diagnosis at 11–26 weeks (early and middle periods of fetal development) has shown a large proportion of T8, T9, T22, T14, T16, T20, T17 and T15 in the structure of prenatally diagnosed abnormalities, but of all those mentioned only T8, T9, T22 have been classified into separate syndromes [6].

Special mention in this context should be made of the cases of full regular trisomy 17. In known reputable sources, directories, guides, manuals, and electronic databases (PubMed, Medline, OMIM) we have not found any description of phenotype for fetus with regular trisomy 17 (only cases of mosaic trisomies 17 are specified) [7, 8].

2. Aim of research

To determine the frequency and mortality of regular trisomy 17 based on the cases we were fixing through our multi-year research, and to describe a symptom- complex of fetal abnormalities that are typical for regular full trisomy 17.

3. Materials and Methods

To meet our targets for the period of 1997 through 2016, we formed groups and made karyotyping of 1808 samples of miscarriages concept products, randomized group of 1572 medical induced abortions at 5–11 weeks of gestation; 9689 samples of invasive prenatal tests done between 11 and 24 weeks of pregnancy (1329 chorionic villus biopsies, 2240 placental biopsies, and 6120 samples of amniotic fluid) - total 13069 samples from women inhabiting south-east and central regions of Ukraine.

Prenatal ultrasound examinations were performed in the 1-st trimester pregnancy to identify the missed miscarriage, as well as in the periods of 11–14 weeks and 18–22 weeks of gestation with ultrasound systems HDI-3000 “ATL/Philps” (USA) and Voluson 730-Pro “General Electric” (USA). Prenatal invasive procedures were controlled using ultrasound scanners SSA-250 “Toshiba” (Japan) and R-3 “Samsung-Medison” (Korea). After elimination of abnormal fetuses with chromosomal aneuploidy, autopsy of abortus was done.

For the analysis we applied GTG (method for differential staining), and we used research microscopes Axioimager A1 “Zeiss”, “Olimpus” BX41, Aristoplan “Leitz” to analyze chromosome spreads . Notice also that we met testing standard for chromosome spreads [9], evaluating no less than 30 metaphase plates.

4. Results

We have found that the proportion of T21, 18, and 13 in pre-embryonic period generally accounts for only 6.33 %, while that of rare trisomy – 93.67 %. Among pregnancies terminated in embryonic period of 5 to 11 weeks, the proportion of rare autosomal trisomies made up 88.2 %. In early fetal period of 11–14 gestational weeks, the rare autosome trisomies amounted to only 6.9 %; at 15–22 weeks – 3.83 %; after 23 weeks – 6.68 % (i. e., the average proportion of rare autosomal trisomies in the fetal group of early, middle and late period made 5.8 %).

The frequency of full T17 in all miscarriages was 1/152 and in medical induced abortions – 1/524; the population frequency of T17 in the first trimester accounted for 1/454. In the process of study we have found that the proportion of trisomy 17 in autosomal trisomy structure varies in different periods of fetal development (**Table 2**).

Specifically, in the group of first trimester miscarriages, T17 proportion averaged 1. 17 %. There were recorded 6 cases of full regular T17 (1 of anembryonic gestation and 5 with embryos which stopped growing), and 2 cases of mosaic T17 combined with polyploidy (one of them with double T17, karyotype: 94, XXXX, +17+17/47, XX+17 mos, the second one – with karyotype: 70, XXX+17/ 47, XX+17 mos) both of anembryonic gestation. In all these cases, pregnancy stopped developing at 5–9 weeks. When performing prenatal testing, we revealed 4 cases of trisomy 17 (**Table 3**) that represented 0.58 % of autosomal trisomies among fetus of 11–22 gestational weeks.

Table 2

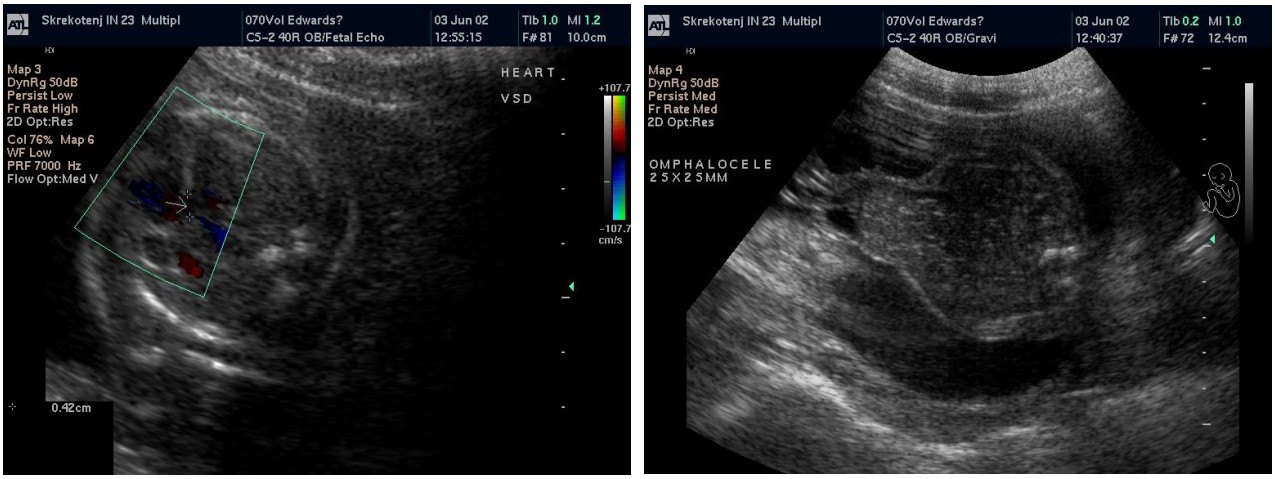
Proportion of T17 in structure of autosomal trisomies in different periods of fetal development

Chromosomal abnormality	Miscarriages Pre-embryonic stage (prior 5 weeks)	Miscarriages 5–11 wks	Prenatal diagnostic 11–14 wks	Prenatal diagnostic 15–22 wks
Trisomy +17	1 (0,79 %)	5 (1,53 %)	1 (0,43 %)	3 (0,72 %)

Table 3

Features of pregnancy with prenatally detected trisomy 17

№	Maternal age	Gestational age (wks)	Ultrasound findings	Karyotype
1	23	22	Prenatal hypoplasia, ventricular septal defect, 'lemon'-shaped head, omphalocele, flexor position of hand, 'rocker-bottom' foot, umbilical cord cyst (**Fig. 1, *a, b***)	47,XX+17
2	17	19-20	Prenatal hypoplasia, nasal bone hypoplasia, brachycephaly.	47,XY+17
3	24	11	Exencephaly,omphalocele,spine deformation and shortening, feet deformation (**Fig. 2**)	47,XY+17 (**Fig. 3**)
4	24	20	Prenatal hypoplasia, severe hydrocephalus, facial dismorphism, nasal bone hypoplasia, complicated cardiac defect, abnormal limbs length (bilateral talipomanus, radial bone aplasia, flexion deformity of hand, unilateral abnormality of lower limb, fibula bone aplasia) spine deformity, small-sized omphalocele (**Fig. 4, *a–e***)	47,XY+17



a *b*

Fig. 1. Echograms of fetus with the full trisomy 17 at 22 weeks of gestation:
a − Transaxial section through the fetal thorax and heart (four-chamber view), ventricular septal defect; *b* − Transaxial section through the fetal abdomen; anterior wall defect: omphalocele

In one case (№ 3) a fetus had severe malformations (**Fig. 2**), similar to ADAM-complex (sequence of amniotic bands), but meticulous ultrasound screening did not detect any manifestations of amniotic bands. Given these abnormalities, there were performed a prenatal differential diagnosis for thoracoabdominal syndrome, OEIS-complex (omphalocele-extrophy-imperforate anus − spinal defects), and with less potential trisomies of chromosomes 18 and 13 that necessitated the prenatal karyotyping which revealed the trisomy 17 (**Fig. 3**).

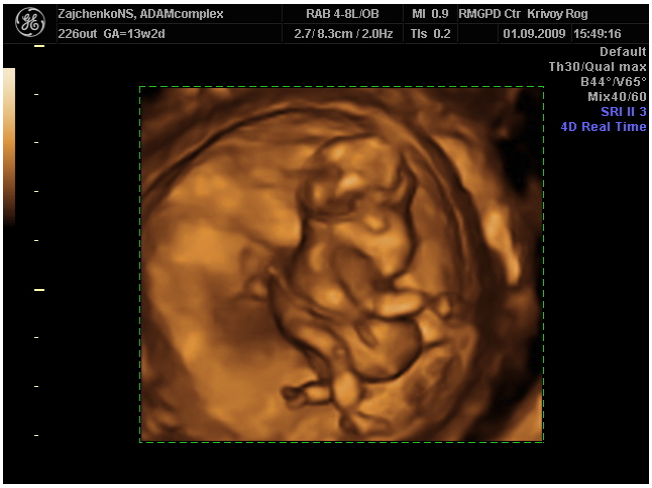


Fig. 2. 3D echography surface reconstruction of the fetus with the full trisomy 17 at 11 weeks of gestation. Multiple congenital anomalies: exencephaly, omphalocele, spine shortening and deformation, feet deformation

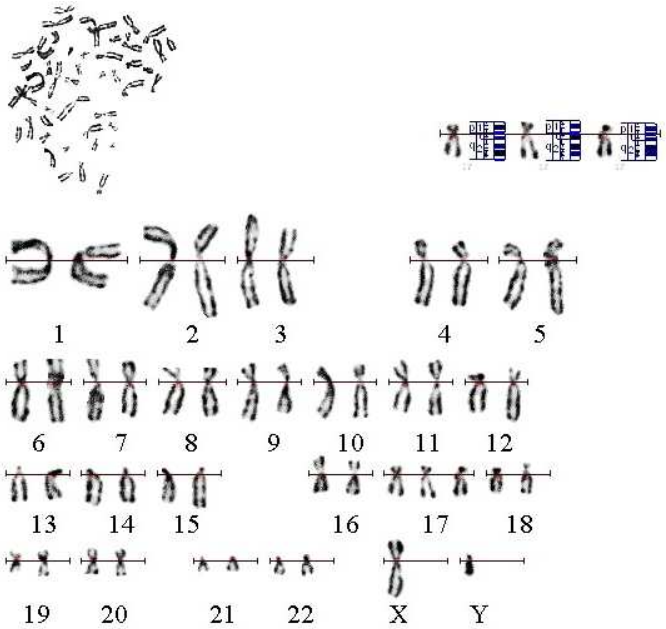


Fig. 3. Karyogram of the fetus at 11 weeks of gestation in Chorionic villus sampling material: 47, XY + 17 (10X100 increase; software "Video Test Karyo 3.1")

In one case (№ 4) the prenatal differential diagnosis was made with TAR syndrome, which had been excluded, because the fetus had no manifestations of anemia. In addition to fetal abnormalities detected by ultrasound (**Fig. 4, *a*–*e***) and later confirmed by autopsy (**Fig. 5, *a, b***), there have been also found such dysmorphic disorder of face as hypertelorism, horizontal eye slits, wide and deep nasal bridge, and mild retromicrognathia.

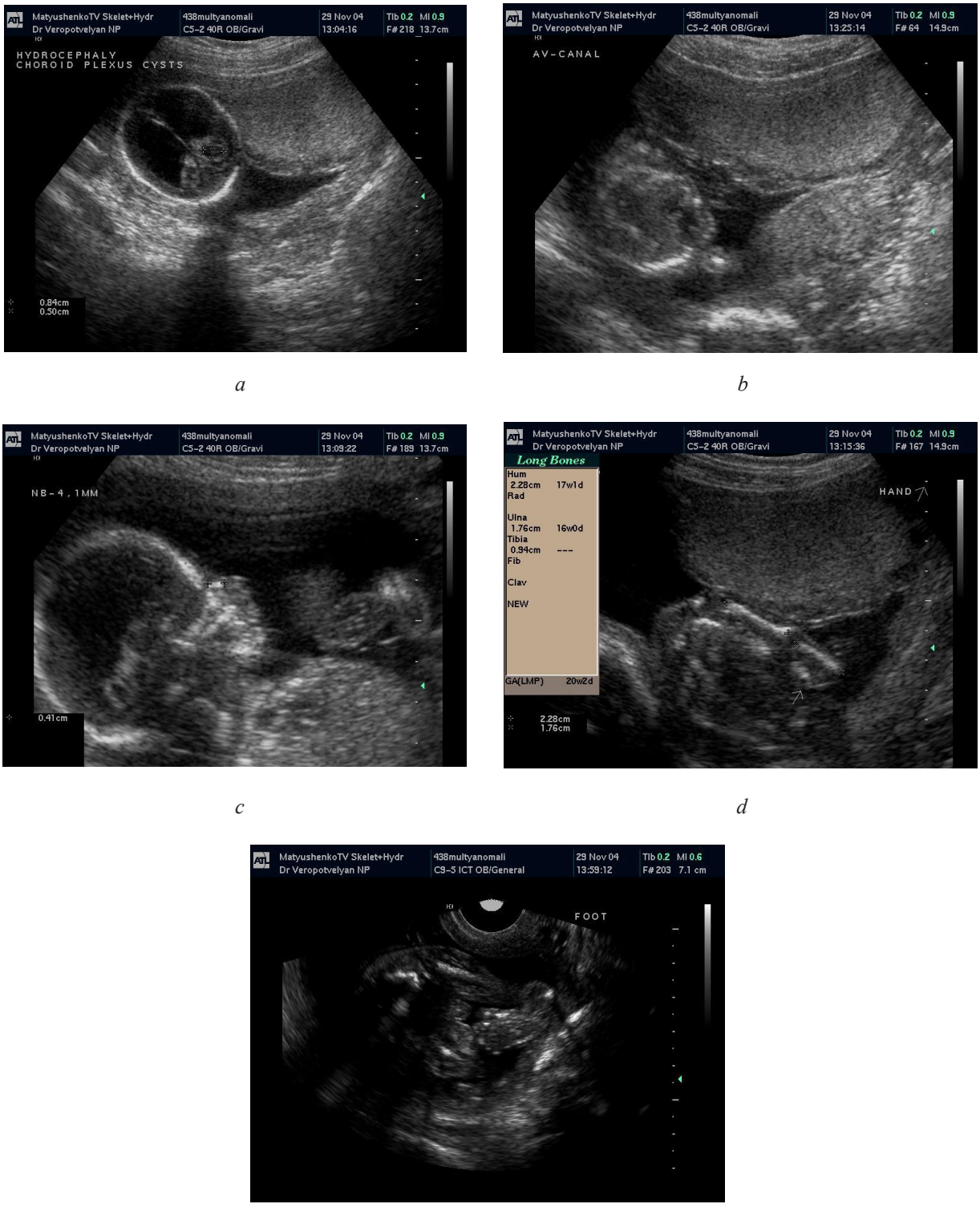
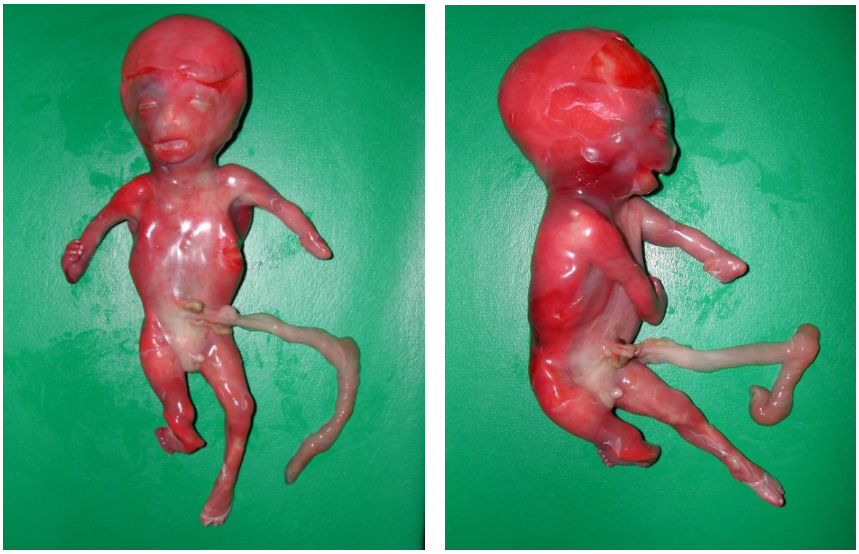


Fig. 4. Echograms of fetus with the full trisomy 17 at 20 weeks of gestation:
a − transaxial section through the fetal head: hydrocephaly, choroid plexus hypoplasy and cysts;
b − Transaxial section through the fetal thorax and heart. Abnormal four-chamber view:
horisontal cardiac axis,complete atrio-ventricular channel; *c* − sagittal section of the fetal face:
high forehead,deep nasal bridge, nasal bone hypoplasia, mild microretrognathy;
d − sagittal section through the fetal upper limb: radiation clubhand, due to radial bone aplasy;
e − transverse section of the deformed foot



a *b*

Fig. 5. Aborted fetus with the full trisomy 17 at 21 weeks of gestation. (Phenotype description in the text): *a* − front view; *b* − side view

Based on ultrasound and postmortem examinations, we have formed a symptom-complex of abnormalities which are typical of full regular trisomy 17 (**Table 4**).

Table 4

Symptom-complex of abnormalities which are typical of full regular trisomy 17

Anatomo-morphological structures	Anomalies/features
Shape of the head	Brachycephalic (1) 'Lemon' (1)
Central nervous system	Exencephaly (1) Hydrocephalus (1) Cerebellum hypoplasy (1)
Facial dismorphism	Hyperthelorism (1) horizontal eye slits (1) wide nasal bridge (1) nasal bone hypoplasia (2) retromicrognathy (1)
Heart	Atrio-ventricular channel (1) Ventricular septal defects (1)
Anterior abdominal wall	Omphalocele (3)
Spinal column	Shortening and deformity (1)
Limbs − tubular bones	Bilateral aplasia of the radial bones (1) &unilateral fibula aplasia (1)
Hands and feet	Flexion deformity (2/3)
Fetal growth (bioparameters)	Prenatal hypoplasia: retardation from gestational age (3)
Umbilical cord	Cyst (1)

As can be seen from the nature of the anomalies we have specified in the recorded cases, complete trisomy 17 is characterized by multiple non-inducing each other development abnormalities in the different anatomo-morphological systems which are derived from ectoderm and mesoderm, that allows us to regard the described symptom-complex as a syndrome.

5. Discussion

Full regular T17 fall within lethal AD and have never been observed among born-alive infants, that is also agrees with Hsu L. Y's findings on T17 being found only among spontaneous abortions with 0.1 %-frequency [10].

Worldwide scientific literature points to descriptions of only 29 prenatally diagnosed cases of mosaic T17, of which only 9 (31.03 %) had abnormal ultrasound findings correlated with a high percentage of mosaic trisomic clones in cell culture of amniotic fluid that ranged from 23 % to over 50 % [8].

All these cases had adverse pregnancy outcomes and included the following ultrasound findings: fetal growth delay (prenatal hypoplasia), cerebellar hypoplasia and/or cerebellar vermian hypoplasia, ventriculomegaly, nuchal cystic hygroma, nuchal thickening, congenital heart disease (ventricular septal defect), pleural effusions (hydrothorax), vertebral anomaly, abnormal limb length, foot deformity, and single umbilical artery. Among postnatal findings, in most cases, there were also described hypoplasia of cerebellum, facial dismorphism, ventricular septal defect, body asymmetry and tibial length differences, in two cases – inguinal hernia and postaxial polydactyly, by one case of kyphoscoliosis, duodenal atresia, intestinal malrotation, cardiomyopathy, ventriculomegaly and hydrocephalus. Further, in some cases were recorded neuropsychiatric development, peripheral neuropathy, hearing and vision loss, and growth delay. Life expectancy of children with mosaic trisomy 17 ranged from 9 days to 9 years. Baltensperger A. produced a summary of pre- and postnatally described all phenotypic signs and symptoms of mosaic T17 with some additional features from their own observation over this chromosome [7]. According to these and other authors [7, 8], big differences in phenotypic features of fetus and infants with mosaic T17 should be explained by different percentage of mosaic abnormal cell clones, their different presence in a variety of anatomical and morphological tissue and moderate-sized sample of observations. As noted above, in most cases of mosaic T17 described in various sources, there were no anomalies both in pre- and postnatal period, and they all ended with a natural birth [8].

In such cases, to confirm mosaic T17, complementary to chromosomal analysis of amniotic fluid cultures, there was performed a cytogenetic analysis of blood lymphocytes and fibroblasts of neonates that recognized as 'gold' standard, [7]. However, the level of mosaicism varies greatly in different tissues and does not correlate with prognosis [11–20]. Molecular genetic analysis has confirmed mosaic T17 in several cases resulted from postzygotic mitotic errors in distribution of maternal chromosome 17 [13, 16, 18]. Parental origin of extra chromosome 17 was determined with genome-wide SNP-microarray molecular genetic analysis [11].

The phenotypic portrait of fetuses with full regular T17 that we described also included prenatal hypoplasia, hypoplasia of cerebellum, facial dysmorphism, hydrocephalus, heart septal defect, abnormal spine, asymmetric abnormalities of long bones, and foot deformities. But the distinctive feature of symptom-complex of full T17 in our description is the presence of omphalocele in 3 of 4 fetuses and umbilical cord cyst in one of them. Thus, the detected signs allowed us to describe a phenotypic portrait of previously undescribed syndrome of full trisomy 17.

6. Conclusions

1. Frequency of full trisomy 17 in all miscarriages was 1/152 and in medical induced abortions − 1/524; the population frequency of T17 in the first trimester accounted for 1/454.

2. Trisomy 17 represented 1,17 % of all autosomal trisomies among embryos at 5−11 gestational weeks and 0,58 % only of autosomal trisomies among fetuses of 11−22 gestational weeks.

3. The symptom-complex of regular full trisomy 17 second trimester fetuses includes central nervous system anomalies, facial dismorphism, cardiac septal defects, omphalocele, limbs anomalies, prenatal hypoplasia, and asymmetry.

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