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Miscarriages after Natural Conception & IVF: Comparative Study of Genetic Analysis of Products of Conception

Elena V. Kudryavtseva [1, 2, *], Sergey N. Fedenev [1], Ilia V. Kanivets [2], Anastasiya N. Troitskaya [1], Vladislav V. Kovalev [3]

1. Ural State Medical University, Yekaterinburg, Russia; E-Mails: ekud2019@gmail.com; onde.trodde@gmail.com; stusya27@gmail.com
2. Genomed LLC, Moscow, Russia; E-Mail: dr.kanivets@genomed.ru
3. Ural Institute of Healthcare Management Named after. A.B. Blokhin, Russia; E-Mail: vvkovalev55@gmail.com

* **Correspondence:** Elena V. Kudryavtseva; E-Mail: ekud2019@gmail.com

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Abstract

Assisted reproductive technologies (ART), including in vitro fertilization (IVF), are modern medical technologies widely used in developed countries. A frequent complication of pregnancy resulting from ART is miscarriage. The leading cause of miscarriage, both sporadic and recurrent, is chromosomal abnormalities (CA) of the embryo. To compare the frequency and structure of chromosomal abnormalities (CA) of the embryo during miscarriages after IVF and natural conception. Retrospective cohort comparative study. The study, conducted in 2018-2022, included 1,000 products of conception (POCs) samples from patients with miscarriage. The study participants were divided into 2 groups depending on the origin of pregnancy: group 1 – women whose pregnancy occurred naturally (n = 862), group 2 – women whose pregnancy occurred as a result of in vitro fertilization (IVF) (n = 138). Miscarriage was confirmed by ultrasound performed at 6-10 weeks of pregnancy. A genetic study of POCs was carried out using chromosomal microarray analysis (CMA). In total, CA was detected in 580

samples (58%), and a normal molecular karyotype was determined in 420 (42%). CAs in abortive material during pregnancy loss are detected with a frequency of 59.05% in cases of natural conception and with a frequency of 51.05% in pregnancies resulting from IVF (p = 0.093). There were no statistically significant differences in the frequency and structure of CA in the study groups. Autosomal trisomies were most often detected. In our study, among all autosomal trisomies, the most common were trisomy 16, trisomy 22 and trisomy 15. Among the sex chromosome abnormalities, monosomy X was most often detected - in total, it was determined in 66 (6.6%) samples, which significantly exceeds the frequency of monosomy X among live births. Only in 0.2-0.3% of cases, when the embryo has monosomy X, pregnancy progresses and ends in a live birth. Copy number variations (CNVs) were often detected - a total of 52 (5.2%) samples with different CNVs, respectively 46 (5.3%) and 6 (4.3%) in groups 1 and 2. Detection of such abnormality is critically important, as it can be the result of carriage of a balanced CAs in one of the parents, which significantly increases the risk of miscarriage in the future. In pregnancies resulting from IVF, mosaicism in abortive material was more common, but the differences were not statistically significant. In group 1, mosaicism was detected in 66 (7.6%) cases and in group 2 - 13 (9.4%) cases. The IVF procedure does not increase the risk of CA in the embryo but also does not significantly reduce it. Considering the high frequency of CA in miscarriage, persons referred for IVF and with a history of idiopathic recurrent pregnancy loss should be informed about the possibility of PGT.

Keywords
Recurrent pregnancy loss; IVF; PGT; chromosomal microarray analysis; miscarriage

1. Introduction

Assisted reproductive technologies (ART), including in vitro fertilization (IVF), are modern medical technologies that are widely used in developed countries of the world [1]. Although IVF technology has been used for more than 40 years [2], there are still some concerns that they may affect the health of future children, and that the incidence of pregnancy complications is higher (compared to natural conception).

The question of the safety of using ART remains open. For example, in the work of Z.S. Zyuzikova et al. (2018), it was demonstrated that children born through the IVF procedure more often suffer from chronic diseases and are less resistant to the action of infectious agents [3]. It is known that the incidence of preterm birth is also higher in pregnancies achieved through ART [4].

A frequent complication of pregnancy resulting from ART is miscarriage [5]. The leading cause of miscarriage, both sporadic and recurrent, is chromosomal abnormalities (CA) of the embryo [6-8]. There are some studies indicating that IVF technology increases the risk of congenital malformations and CA in the embryo [9, 10].

Genetic analysis of products of conception (POCs) from a miscarriage can provide information about the cause of pregnancy loss. It also helps to determine whether more testing is required during the next preconception. The preferred methods for studying POCs in cases of miscarriage are array comparative genomic hybridization (aCGH - array comparative genome hybridization) or

chromosomal microarray analysis (CMA) [11]. These methods have several advantages compared to standard cytogenetic research (karyotyping) - they determine signs of contamination with maternal blood, do not require cell cultivation, and reduce the likelihood of obtaining a false result [11, 12]. In addition, with karyotyping, it is impossible to detect submicroscopic segmental aneuploidies, including clinically significant ones [13].

The *objective* was to compare the frequency and structure of chromosomal abnormalities (CA) of the embryo during miscarriages after IVF and natural conception.

2. Material and Methods

Study design: retrospective cohort comparative study.

The study, conducted between 2018 and 2022, included 1,000 cases of POCs from patients with miscarriage.

Criteria for inclusion in the study: singleton pregnancy, presence of ultrasound criteria of miscarriage, gestational age 6-10 weeks, consent to participate in the study, availability of the result of CMA of POCs.

Non-inclusion criteria: the presence of severe somatic pathology in a pregnant woman, an acute inflammatory or infectious disease during pregnancy, the presence of established genetic abnormalities in a couple, the use of donor gametes during ART, pre-implantation genetic testing (PGT) of the embryo, multiple pregnancies.

Exclusion criteria: refusal of the patient to participate in the study, contamination of biological material with maternal blood and impossibility of conducting genetic analysis of POCs.

The study participants were divided into 2 groups depending on the origin of pregnancy: Group 1 – women who became pregnant naturally (n = 862), and Group 2 – women who became pregnant due to IVF (n = 138). All study participants were Caucasian.

Miscarriage was diagnosed by ultrasound, performed at 6-10 weeks of pregnancy, which revealed the absence of cardiac activity in the embryo. After the diagnosis was established, the patients underwent manual vacuum aspiration of the contents of the uterine cavity. The resulting POCs (chorion villi) were placed in a 0.9% sterile physiological solution (at least 0.5 cm^2) and sent for analysis to the genetic laboratory per recommendations for the transportation of biological material. A genetic study of chorionic villi was carried out using chromosomal microarray analysis (CMA). To carry out SNP-based CMA, the Genoscan 3000 system was used (RC No. FSR 2010/08511 dated August 11, 2010) according to the manufacturer's protocol on oligonucleotide microarrays containing 2 types of markers with a resolution of ~500 kb.

Statistical analysis was carried out using StatPlus: Mac 8.0.3 (AnalystSoft, USA). Among the methods of descriptive statistics, the arithmetic mean and standard deviation (M ± SD) are given - for the age of the study participants (the distribution corresponded to normal), absolute and relative frequencies (%) for nominal characteristics. To compare the study groups in terms of the frequency of occurrence of various CAs in the embryo, analysis of contingency tables and the χ^2 test were used. The odds ratio (OR) was also calculated. Critical value of the significance level (p) was taken equal to 0.05.

3. Results

The clinical characteristics of the study groups are presented in Table 1.

Table 1 Clinical characteristics of the study groups.

Parameter	Group 1 (n = 862)	Group 2 (n = 138)	p
Age, years	34.2 ± 5.5	35 ± 4.8	0.437
Average Gestational age	7 weeks 3 days (52 ± 15 days)	7 weeks 5 days (54 ± 14 days)	0.671
history of miscarriage	318 (36.89%)	49 (35.5%)	0.754

Chromosomal abnormality was detected in 580 samples (58%), and a normal molecular karyotype was determined in 420 (42%). The distribution of various groups of chromosomal abnormalities identified in the abortion material of study participants is shown in Figure 1.

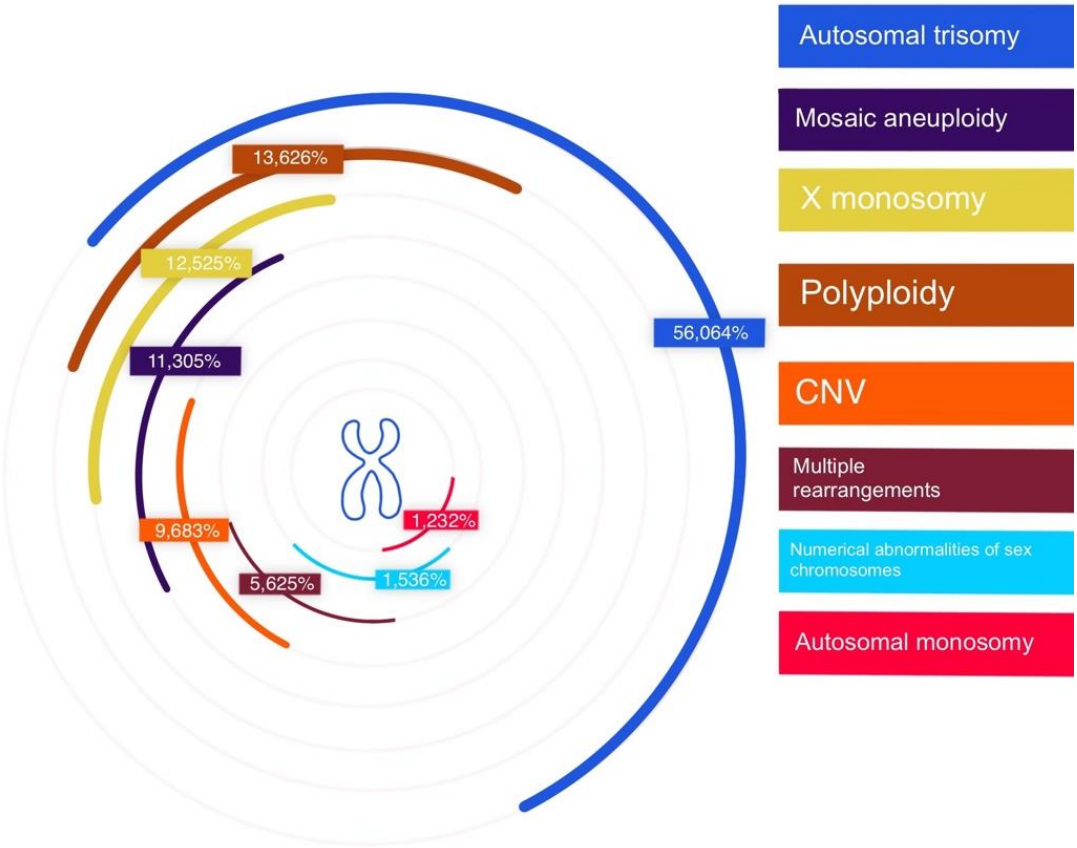

Figure 1 Types of chromosomal abnormalities in abortive material during miscarriage (among samples with CA).

Results of the study of POCs using CMA and comparison of the study groups for various types of chromosomal abnormality are shown in Table 2. No statistically significant differences in the frequency and structure of CAs were found in the study groups.

Table 2 Results of the study of abortive material using CMA in both groups.

Result	Group 1. Абс. (%)	Group 2. Абс. (%)	χ^2	p	OR
Normal molecular karyotype	353 (40.951)	67 (48.55)	2.82	0.093	0.734 (0.512-1.053)
Autosomal trisomy (T)					
T1	0	0	-	-	-
T2	5 (0.58)	1 (0.724)	0.041	0.838	1.251 (0.145-10.79)
T3	2 (0.232)	1 (0.724)	0.965	0.325	3.138 (0.28-34.85)
T4	11 (1.276)	1 (0.724)	0.305	0.58	0.564 (0.072-4.408)
T5	1 (0.116)	1 (0.724)	2.207	0.137	6.284 (0.39-101.071)
T6	3 (0.348)	0	0.481	0.487	2.09 (0.215-20.237)
T7	9 (1.044)	2 (1.449)	0.179	0.671	1.393 (0.297-6.52)
T8	9 (1.044)	0	1.453	0.227	9.691 (0.086 -5.503)
T9	11 (1.276)	1 (0.724)	0.305	0.58	0.564 (0.072-4.408)
T10	2 (0.232)	0	0.32	0.571	3.138 (0.282-34.85)
T11	2 (0.232)	0	0.32	0.571	3.138 (0.282-34.85)
T12	3 (0.348)	0	0.481	0.487	2.09 (0.215-20.237)
T13	16 (1.856)	1 (0.724)	0.911	0.339	0.385 (0.05-2.933)
T14	9 (1.044)	2 (1.449)	0.179	0.671	1.393 (0.297-6.52)
T15	28 (3.248)	4 (2.898)	0.046	0.828	0.889 (0.306-2.575)
T16	55 (6.38)	6 (4.347)	0.858	0.354	0.666 (0.281-1.58)
T17	4 (0.464)	0	0.642	0.687	1.565 (0.173-14.112)
T18	9 (1.044)	2 (1.449)	0.179	0.671	1.393 (0.297-6.52)
T19	1 (0.116)	0	0.16	0.137	6.284 (0.39-101.071)
T20	5 (0.58)	4 (2.898)	7.169	0.007	5.116 (1.356-19.294)
T21	30 (3.48)	6 (4.347)	0.257	0.611	1.26 (0.514-3.086)
T22	31 (3.596)	6 (4.347)	0.188	0.664	1.218 (0.498-2.976)
Mosaic aneuploidy					
Mosaicism	55 (6.38)	10 (7.246)	0.146	0.701	1.146 (0.569-2.306)
Multiple rearrangements					
Multiple rearrangements	36 (4.176)	2 (1.449)	2.42	0.119	0.337 (0.08-1.417)
Numerical abnormalities of sex chromosomes					
X monosomy	58 (6.728)	8 (5.797)	0.167	0.684	0.853 (0.398-1.827)
XXX	2 (0.232)	0	0.32	0.571	3.138 (0.282-34.85)
XXY	5 (0.58)	1 (0.724)	0.041	0.838	1.251 (0.145-10.79)
Copy number variations (CNVs)					
CNV	46 (5.336)	6 (4.347)	0.235	0.814	0.806 (0.337-1.925)
Autosomal monosomy (M)					
M21	3 (0.348)	1 (0.724)	0.423	0.515	2.09 (0.215-20.237)
M18	1 (0.116)	0	0.16	0.688	6.284 (0.39-101.071)
Polyploidies					

Triploidy	57 (6.612)	5 (3.62)	1.827	0.176	0.531 (0.209-1.349)
Tetraploidy	3 (0.348)	0	0.481	0.487	2.09 (0.215-20.237)
Total result					
CA	509 (59.048)	71 (51.449)	2.82	0.093	0.734 (0.512-1.053)
Total	862 (100)	138 (100)	-	-	-

Autosomal trisomy (T) was most frequently detected (Figure 2). In our study, T16 was the most common, T22 was the second most common, and T15 was the third. This is consistent with the scientific literature data presented earlier [6, 14-16]. T16 is the most common cause of miscarriage. Back in 2005, in an analysis of the spectrum of chromosomal abnormalities, it was identified as the most common type of trisomy in spontaneous abortions [17]. Despite the use of different methods of genetic analysis, in this study, the analysis of POCs was carried out using standard karyotyping and not using CMA, and our results are consistent with the literature data. T16 is not compatible with live birth, as is T15. Things are somewhat different with T22 - live birth is sporadic in the presence of T22, but the average life expectancy is several days. With the mosaic variant T22, life expectancy can be calculated in years, but in such people, many developmental defects and a pronounced delay in motor and psycho-speech development in the postnatal period have been described [18-20].

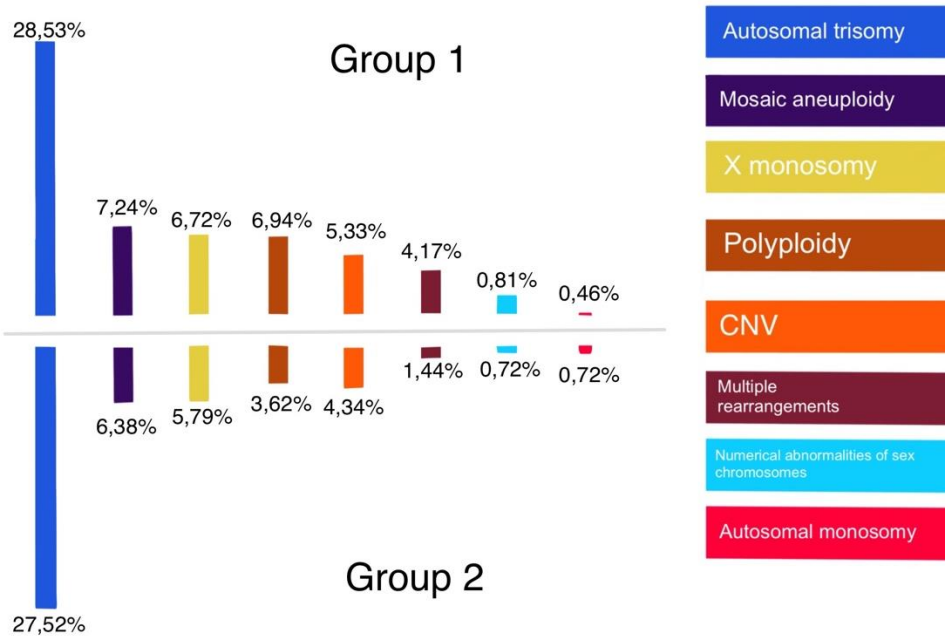

Figure 2 The frequency of occurrence of different CAs in research groups.

Among the abnormalities of sex chromosomes, monosomy X (MX) was most often detected - in total, it was determined in 66 (6.6%) samples. This CA in the postnatal period is associated with Turner syndrome. The polysomy of sex chromosomes was found significantly less often - only 8 (0.8%) cases. In no case were the Y-chromosomes dispensed revealed.

In 52 (5.2%) samples, copy number variations (CNV) - respectively, 46 (5.3%) and 6 (4.3%) in groups 1 and 2, were identified. The description of CNV detection is presented in Table 3.

Table 3 Identified CNVs.

№	chr	Location of the fragments	Size (Mb)	Group
1	10	arr10q22.1q26.3(74210295-135427143) × 3	61.217	1
	7	arr7p22.3q11.23(43360-75745033) × 3	75.701	
2	10	arr10p15.3p15.2(100026-3154109) × 3	3.054	1
	10	arr10p15.1q26.3(4190057-135427143) × 3	131.27	
	7	arr7q31.33q36.3(125509933-155536111) × 3	30.026	
3	7	arr7q36.3(155550610-159119707) × 1	3.569	1
	11	arr11q21q23.3(95686785-118172520) × 3	22.485	
	11	arr11q23.3q25(118273018-134938470) × 3	16.665	
4	13	arr13q32.1q32.2(97433283-98805367) × 3	1.372	1
	13	arr13q32.2q34(98832894-115107733) × 1	16.275	
	3	arr3q26.1q29(161130069-197851986) × 3	36.721	
5	9	arr9q34.3(138563158-139427066) × 3	0.864	1
	9	arr9q34.3(140151727-141020389) × 1	0.869	
6	22	arr 22q11.22q11.23(22962961-24953227) × 3	1.99	1
7	Y	arr Yq11.23(27021626-28126699) × 0	1.105	2
8	5	arr 5p15.33p14.3(113576-20500186) × 1	20.387	1
	11	arr11q14.2q25(86457922-134938470) × 3	48.481	1
	8	arr 8p23.3p21.1(158048-28172498) × 1	28.014	
	8	arr 8p21.1p11.22(28085807-38420069) × 1	10.334	
9	8	arr 8p11.22p11.21(38523881-41868806) × 3	3.345	1
	8	arr 8p11.21q22.3(42076045-102141671) × 3	60.066	
	8	arr 8q22.3q24.13(101961761-124129195) × 3	22.167	
	8	arr 8q24.3(142484529-146295771) × 3.	3.811	
10	Y	arr Yq11.223q23(24493072-28,423,925) × 0	3.931	1
	8	arr 8p23.3p12(158048-32312485) × 1	32.154	
11	8	arr8p12p11.21(32541215- 40036626) × 1	7.495	1
	8	arr8q21.3q24.3(91128636-146295771) × 3	55.167	
12	Y	arr Yq11.223q23(24663585-28382367) × 0	3.719	1
13	1	arr 1q21.1q21.2(147743035-146511925) × 3	1.231	1
	X	arr Xp22.33p22.13(1805617-18266492) × 1	16.46	
	X	arrXp22.13p11.4(17989269-38370319) × 1	20.381	
14	X	arrXp11.4(38372500-41850200) × 1	3.478	1
	X	arrXp11.4p11.3(41876219-44887450) × 1	3.011	
	X	arrXp11.3p11.22(45464472-50621,872) × 1	5.158	
15	7	arr 7q31.1q36.3(114123307-159119707) × 1	44.996	1
16	15	arr 15q11.2(22770421-23291159) × 1	0.521	1
17	8	arr 8p23.3p23.1(158048-7044046) × 1	6.886	1
	8	arr8p23.1q24.3(12527948-146295771) × 3	133.767	
18	X	arrXp22.31(6486489-7676903) × 1	1.190	1
19	22	arr 22q11.23(23652586-25041592) × 3	1.389	1
20	14	arr14q11.2(20516277-23178110) × 3	2.661	2

	14	arr14q11.2q32.33(23575627-107284437) × 3	83.709	
21	15	arr15q15.3(4389121-44968229) × 1	1.079	1
22	4	arr4p16.3p16.2(68345-5541650) × 1	5.473	1
	16	arr16p13.11(14897804-16521281) × 3	1.623	
23	17	arr17q23.3(61883437-81041823) × 2	19.158	2
24	1	arr1q21.1(145157447-162000761) × 3	16.843	1
25	10	arr10q26.13q26.3(126761642-135426386) × 3	8.665	1
	19	arr19p13.3p13.2(260911-11888538) × 1	11.627	
26	3	arr 3q11.1(93119464-93720854) × 1	0.601	1
27	1	arr1p22.2p21.3(90785240-95819015) × 1	5.034	1
28	3	arr3p26.3p22.3(61891-32304103) × 3	32.242	1
	7	arr7q32.3q36.3(131911428-159119707) × 1	27.208	
29	X	arrXp22.31(6558520-7690001) × 1	1.131	1
30	2	arr2q32.3q33.1(197286613-198800532) × 1	1.514	1
31	Y	arrYq11.223q11.23(25844773-27811878) × 0	1.967	2
32	7	arr7p22.3p21.3(43360-12239274) × 1	12.196	1
	15	arr15q26.1q26.3(92171924-102429112) × 3	10.257	
33	2	arr2q13(111406072-113049098) × 3	1.643	1
34	15	arr15q11.2(22770421-23276605) × 1	0.506	2
35	8	arr8p23.3p21.2(158048-27300621) × 1	27.142	1
36	6	arr6p25.1p22.3(6076432-19828213) × 1	13.751	1
37	15	arr15q11.2(22770421-23276605) × 1	0.506	1
38	4	arr4q32.1q35.2(160823973-190957473) × 3	30.133	1
	14	arr14q11.2q24.3(20511672-76781841) × 3	56.270	1
39	7	arr7q36.2q36.3(154963262-159076960) × 1	4.114	1
	12	arr12q22q24.33(95944259-133777562) × 3	37.833	
40	2	arr2q37.3(242423912_242983384) × 1	0.559	1
41	2	arr2p21(44581446-46237209) × 1	1.655	1
42	2	arr2p21(44659905-46254750) × 1	1.595	1
43	14	arr14q23.1q32.33(60927247-107285437) × 3	46.358	2
44	15	arr15q11.2(22770421-23654294) × 1,(20) × 3	0.884	1
45	15	arr15q11.2(22770421-23291159) × 1	0.521	1
46	8	arr8p23.2p22(3067723-13909218) × 1	10.841	1
47	22	arr22q11.1q11.21(16888899-19732516) × 1	2.844	1
48	X	arrXq28(150846856-154921519) × 2	4.075	1
49	7	arr7q22.1q36.3(103241632-159119707) × 1	55.878	1
	10	arr10q24.33q26.3(105377475-135427143) × 3	30.05	1
50	16	arr16q23.1q24.2(75622992-87172625) × 1	11.55	1
51	11	arr11p15.5p15.4(230615-4242111) × 3	4.011	1
	11	arr11q13.3q25(69806082-134938470) × 3	65.132	
52	1	arr1p32.3p32.2(55218154-56972400) × 3	1.754	1

In some cases, mosaic abnormalities were determined. In our work, among cases of natural pregnancy, mosaicism was discovered in 66 cases - this is 7.6% of all samples, 13% monitoring the

samples with CAs in this group. Among the cases of IVF, mosaicism was revealed in 13 cases - respectively 9.4% and 18.3% of all cases and among the CAs. During the pregnancy that occurred as a result of IVF, mosaicism in POCs was detected more often, but the differences were not significant. Mosaic trisomies of 2, 3, 6, 7, 8, 9, 13, 15, 16, 17, 20 and 22 chromosomes were identified. Most often, in chorionic villi, there was a mosaicism in trisomy 16.

4. Discussion

We consider that the most significant result of our study is that we demonstrated the absence of statistically significant differences in the frequency and structure of CAs in biological material during miscarriage when compared depending on the genesis of pregnancy. In both groups, CA was detected in more than half of the cases (59% and 51.4% in groups 1 and 2, respectively). It can be concluded that the IVF procedure does not increase the risk of CA in the embryo but also does not significantly reduce it. For obvious reasons, the exception to this conclusion will be cases of ART, the implementation program of which involved preimplantation genetic testing for aneuploidy (PGT-A). However, these cases were not included in the study groups, being one of the non-inclusion criteria. Similar results were obtained by a group of Russian researchers in 2014 [21]. However, unlike our work, the standard karyotyping method was used in this study. We consider it important to demonstrate that when using a more modern research method (CMA) there are also no differences between the study groups.

Over the past 10 years, the issue of whether it is advisable to refer women with idiopathic recurrent pregnancy loss to IVF has been actively discussed. In Russia, the provision of medical care for problems with miscarriage does not involve sending a patient with a primary miscarriage and her partner, whose family history does not indicate the presence of CA, to preimplantation genetic diagnosis of the embryo [22]. The European clinical guidelines “Recurrent pregnancy loss” (2022) state that PGT-A is not a cost-effective strategy for increasing the rate of live births [11]. This conclusion was made on the basis that previous studies have shown that even though PGT-A slightly reduces the likelihood of early pregnancy loss (with a “biochemical” pregnancy) and increases the probability of live birth when calculating the number of embryo transfers (ET), this procedure did not lead to a significant increase in live births when calculating the total number of patients in IVF programs [23]. In addition, data on the use of PGT-A for miscarriage are limited [11]. At the same time, if, in addition to miscarriage, there are indications for referring partners for IVF (infertility in a couple), we believe that patients should be informed about the possibility of PGT-A to reduce the risk of pregnancy loss.

Our work showed that autosomal trisomy, especially trisomy 16, 22, and 15, are most often detected among CAs. These results are consistent with previous studies [6, 8, 16]. The novelty of our study was that patients who became pregnant due to IVF were allocated to a separate group, and similar results were obtained in this group.

Monosomy X was detected in abortive material in a total of 66 (6.6%) study participants. In the postnatal period, monosomy X (Turner syndrome) occurs with a frequency of only 25-50:100,000 women [24, 25]. Thus, only in approximately 0.2-0.3% of cases, when the embryo has monosomy X, pregnancy progresses and ends in a live birth. Considering these data, as well as the pronounced clinical picture of Turner syndrome, we believe that ET cannot definitely be recommended when determining monosomy X during PGT-A.

As mentioned above, polysomy of sex chromosomes was determined in miscarriage much less frequently than monosomy X. The presence of three copies of the X chromosome (karyotype 47, XXX) was determined only in 2 (0.2%) samples. Both of them were obtained from women with spontaneous pregnancy. Trisomy X syndrome in the population occurs with a frequency of 1:1000 newborn girls (in the general population - 0.05-0.1%) [26]. The presence of two copies of the X chromosome and one Y chromosome was determined in 6 (0.6%) samples - 5 (0.58%) and 1 (0.72%) in groups 1 and 2, respectively. Karyotype frequency of 47, XXY (Klinefelter syndrome) accounts for approximately 1:500-1:1000 boys (in the general population, approximately 0.05-0.1%) [26, 27]. Consequently, polysomy of the X chromosome in both male and female karyotypes also increases the risk of miscarriage (in abortive material, such abnormalities occur 5-10 times more often than in live births). However, the chances of a live birth in this case are significantly higher than with monosomy X. There are currently no clear recommendations regarding the possibility of ET with an extra X chromosome. We believe that the transfer of such embryos is possible in the absence of euploid embryos in the IVF program and after counseling the couple with a geneticist and informing them about the clinical manifestations of such CA, as well as the increased risk of pregnancy loss. In no case was a molecular karyotype with an extra Y chromosome (XYY) determined. Likely, this restructuring does not increase the risk of pregnancy loss. Considering the minor clinical manifestations of Y-chromosome disomy in men [26], we believe that if such a karyotype is identified in an embryo, it can be recommended for transfer.

In 65 cases, polyploidy was detected - 62 triploidy and 3 instances of tetraploidy. We assume that the actual number of cases of tetraploidy in miscarriage is significantly higher. However, the definition of tetraploidy is a limitation for CMA [7, 28]. At the same time, the scientific literature indicates that it is incorrect to say that “CMA cannot detect tetraploidy” [29]. Saucier J. et al. claim that using oligonucleotide matrices makes detecting some forms of tetraploidy possible. This method does not detect 2:2 tetraploidy (i.e. karyotype 92, XXXX or 92, XXYY), but is able to detect 3:1 tetraploidy (92, XXXY) [29]. In our work, in all three cases of determining teraploidy, the molecular karyotype was arr(1-22) × 4,(X) × 3,(Y) × 1, which corresponds to the karyotype 92, XXXY. Additional research methods are required to reliably determine the frequency of tetraploidy. Tetraploidy containing two diploid cell lines with a 2:2 set of sex chromosomes cannot be detected by the CMA method [30]. Great difficulties also arise in the presence of tetraploidy/diploidy mosaicism [31]. Therefore, in cases where CMA during a miscarriage does not determine the presence of CA, the FISH method (fluorescence in situ hybridization) is recommended as an additional diagnostic method to detect tetraploidy [30].

Copy number variations (CNVs) were often detected - a total of 52 (5.2%) samples with different CNVs, respectively 46 (5.3%) and 6 (4.3%) in groups 1 and 2. Detection such abnormality is critically important, as it can be the result of carriage of a balanced CAs in one of the parents, which significantly increases the risk of miscarriage in the future [8, 28, 30]. Some CNVs can also affect fertility, such as CNVs of the Y or X chromosomes [32, 33]. The study of W. Huang et al. (2019) explored the correlation between CNVs and female infertility and they showed that autosomal CNVs (for example 22q11.21 duplications) could also affect fertility [33]. Therefore, in some cases, when CNV is detected in abortion material, it is necessary to examine parents for carriage of a similar CNV.

A mosaic karyotype was often determined in the abortive material in both groups. 65 (6.5%) samples with a mosaic karyotype were identified. Moreover, in group 2, mosaicism was detected

more often - in 7.25%. It is essential to know the high probability of chromosomal mosaicism when performing PGT in IVF programs. The Preimplantation Genetic Diagnosis International Society (PGDIS) allows the transfer of mosaic embryos, but those counseled in this case should be warned about the increased risk of pregnancy loss [34].

4.1 Limitations of the Study

Our study analysis of CA was performed on chorionic villi, so it is necessary to consider the possible false positives and negatives when analyzing the material (due to the presence of cells with different karyotypes in embryonic and extraembryonic tissues). In addition, CMA cannot detect low-level mosaicism. Therefore, mosaic CA with a level less than 20-30% of the abnormal clone may have been missed [7]. An abnormal clone can be represented by both aneuploid cells and cells containing CNV.

5. Conclusion

Various chromosomal abnormalities in abortive material during miscarriage are detected with a frequency of 59.05% in the natural genesis of conception and with a frequency of 51.05% in pregnancies resulting from IVF; the differences are not statistically significant. The frequency and structure of chromosomal abnormalities do not depend on the genesis of pregnancy. IVF does not increase the likelihood of CA in the embryo. Considering the high frequency of CA in miscarriage, persons referred for IVF and having a history of idiopathic recurrent pregnancy loss should be informed about the possibility of PGT-A.

Author Contributions

Kudryavtseva EV: Conceptualization, writing – original draft, formal analysis, writing – review and editing. Fedenev SN: writing – original draft, formal analysis. Kanivets IV: Methodology, writing – review and editing. Troitskaya AN: Statistical processing, design of tables and figures, writing – review and editing. Kovalev VV: Conceptualization, writing – original draft, writing – review and editing. All authors have read and approved the published version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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