fortune Journals

Research Article

OBSTETRICS AND GYNECOLOGY RESEARCH

ISSN: 2637-4560

Mosaicism For Autosomal Trisomies: A Review of The Literature Suggests Inverse Effects of Carriers' Gender and Maternal Age on Clinical Manifestations

Natalia V. Kovaleva[1]* and Philip D. Cotter[2]

Abstract

Various clinical aspects of human mosaicism have been thoroughly investigated worldwide for some time. Female predominance among mosaic carriers was reported, but the clinical significance of mosaic carriers' gender was not evaluated. The current study is the first to consider the diverse aspects of male-to-female ratio (sex ratio, SR) variations in somatic diploid/trisomic mosaicism. The data on gender and clinical status of mosaic carriers and maternal age were retrieved for 948 prenatal diagnoses including true fetal mosaicism (TFM) and confined placental mosaicism (CPM), and on 318 cases of postnatally detected mosaicism (PNM). Remarkably, the overall SRs in every study cohort were female-biased, being 0.8 each. However, mosaic trisomies for chromosomes 7, 8, 10, and 20 demonstrated a male prevalence across TFM, CPM and PNM cohorts, unlike to mosaic trisomies 9, 12, 13. 14, 18, 21, and 22 with a female prevalence. We found an apparent predominance of females among abnormal outcomes; 49 males and 73 females (SR=0.67) vs normal 45 males and 41 females (SR=1.1). Further analysis determined a sex-specific negative effect of certain chromosomes involved including chromosomes 2 (male-specific), 4, 9, 11, 12, 18, and 22 (female-specific). Female predominance was observed in cases of intrauterine fetal losses and in cases of intrauterine growth restriction. A higher proportion of advanced maternal age was found in normal outcomes, either male or female mosaic carriers in every studied cohort demonstrating a "positive" effect, opposite to "negative" effect of female gender. The data reported requires further strengthening by collective international efforts.

Keywords: Sex ratio; mosaic autosomal trisomies; prenatal diagnosis; postnatal diagnosis; true fetal mosaicism; confined placental mosaicism; intrauterine growth restriction; fetal loss; advanced maternal age

Introduction

Variations in male to female ratio, both in normal populations and in various abnormal conditions, have always been subject to the attention of researchers. In the field of cytogenetics, sex ratio (SR) among liveborn carriers of the most viable autosomal trisomies for chromosomes 13, 18, and 21 was studied repeatedly since the mid-1960s [1-4]. Later, with rapidly evolving laboratory technologies, it became possible to accumulate data on non-viable trisomies in both products of conception and prenatally diagnosed fetuses [5,6].

However, analysis of the SR among non-mosaic trisomy carriers in these both categories is mostly of limited practical value because prospective parents naturally assume a normal child and rarely consider an option of having an

Affiliation:

[1]Academy of Molecular Medicine, Mytniskaya str. 12/44, St. Petersburg, Russian Federation 191144

[2]ResearchDx, 5 Mason Ln, Irvine, CA 92618

***Corresponding author:**
Natalia V. Kovaleva, Academy of Molecular Medicine, Mytniskaya str. 12/44, St. Petersburg, Russian Federation 191144, Russia.

Citation: Natalia V. Kovaleva, Philip D. Cotter. Mosaicism For Autosomal Trisomies: A Review of The Literature Suggests Inverse Effects of Carriers' Gender and Maternal Age on Clinical Manifestations. Obstetrics and Gynecology Research. 7 (2024): 116-128

Received: October 23, 2024
Accepted: November 04, 2024
Published: November 07, 2024

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

abnormal one. Situation with mosaic trisomies may be different, since there is a chance of having a healthy offspring. Therefore, various clinical aspects of prenatal mosaicism phenomena are being thoroughly investigated and reported in numerous original articles and reviews. Chromosome-specific variations in SR among mosaic carriers were reported [7,8], but the clinical significance of mosaic carriers' gender was not evaluated.

Previous studies demonstrated SR may be considered an effective tool for recognition and examination of pathological processes, and risk prediction. For example, gender appeared to be an essential factor affecting clinical manifestation of chromosomal imbalance and reproductive risks in carriers of segmental mosaicism [9]. Consequently, the goal of this study was a comprehensive analysis of SR among carriers of mosaicism for single autosomal trisomy in prenatal and postnatal diagnoses.

Materials and Methods

We reviewed the same dataset used in a previous publication [10]. The data for this study were obtained from literature identified from various sources including PubMed, Research Gate and ChromosOmics UPD Database [11]. We screened over eight hundred publications on mosaic trisomies for the presence of the data of interest including gender and clinical status of mosaic carriers, maternal age and reproductive history. 596 publications containing data on 948 prenatal diagnoses and 318 postnatal diagnoses were selected for the analysis. Maternal age was reported in 546/948 (57%) prenatally diagnosed cases and 217/318 (68%) postnatally diagnosed cases. Pregnancy outcome was indicated in 796/948 (84%) cases, and parental origin of the euploid line was determined in 179 cases.

Prenatal diagnoses were divided into true fetal mosaics (TFM) and mosaics confined to placenta. According to common practice, mosaicism detected in either direct chorionic villi samples (CVS), or in cultured CVS, or in both, but not in amniocytes, was classified as confined placental mosaicism (CPM). According to another diagnostic approach, where no villus samples were tested, instead, amniocentesis was performed. If mosaicism detected in amniocytes was not confirmed in fetal cord blood, CPM was concluded. Those cases reported to have no confirmatory study (most frequently because of elective termination of pregnancy or miscarriage) or data was not available, fall into the third category; Not confirmed.

Pregnancy outcomes were classified as abnormal when a fetus or newborn had a structural abnormality or multiple abnormalities, as well as dysmorphic features, developmental delay, mental retardation at postnatal follow-up. Isolated intrauterine growth restriction (IUGR) and isolated pigmentary abnormality were not considered as abnormal. Cases with clinical manifestation of UPD were excluded when comparing normal vs abnormal outcomes since these abnormalities did not involve a concomitant mosaicism in most cases.

Additionally. data on 1696 spontaneous abortuses with either nonmosaic or mosaic trisomy of known gender were retrieved from 38 published reports.

Statistical analysis was performed using software: LePAC (https://eris62.eu/ErisLePAC.html) for estimation of 95% confidence intervals (CI) for proportions, their differences and ratios; StatXact (https://www.cytel.com/software/statxact/) for exact point and interval estimation of the parameters of multinomial distribution as well as Fisher-Freeman-Halton test for contingency tables RxC; MOVER-D (https://profrobertnewcomberesources.yolasite.com/) which calculates a confidence interval for a difference of two quantities, starting from independent estimates and confidence intervals for both; Fisher's exact test p-value calculator, 2×2 and 2×3 (https://www.cog-genomics.org/software/stats) which calculates the midp-values for the Fisher's exact tests. Midp is a p value adjusted for the known conservativity of the exact tests.

Results and Discussion

Sex ratio in prenatal and postnatal diagnoses

Data on numbers of males and females according to chromosomes involved are presented in Table 1. It is remarkable that the overall SR in all previously studied cohorts was the same; 0.8 each. However, there is no general consistency regarding male-to-female ratios through TFM, CPM and PNM cohorts for every involved chromosome. For chromosomes 2, 3, 4, 15, 16, 17, we see different male to female ratios between TFM and PNM cohorts. Apparent chromosome-specific consistency is seen for chromosomes 7, 8, 10, 20 with a male prevalence through TFM, CPM and PNM cohorts.

Trisomies 7, 8, and 20 are among the most common mosaic trisomies detected prenatally. MosT7 and mosT8 primarily resulted from mitotic errors [12], and piecing together the strong male predominance among their carriers and mitotic origin of the extra chromosomes, one may hypothesize that Y-bearing sperm can promote postfertilization nondisjunction of maternal chromosomes. Unfortunately, we failed to find data on molecular studies of the parental/cell origin of mosT10 and mosT20.

There was no previously reported study on the origin of mosT9 and mosT12 that demonstrated a female prevalence across TFM, CPM and PNM cohorts, similar to carriers of mosaic trisomies for chromosomes 13, 14, 18, 21, 22 of mostly meiotic origin [12]. The mechanism of mosaicism formation in these trisomies is mostly a loss of one of the trisomic chromosomes resulting in a diploid cell line, biparental or uniparental. This mechanism appeared to be female-specific, as it was suggested by Benn [13] and confirmed later by Kovaleva [14].

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Table 1: Sex ratio in prenatal diagnoses including true fetal mosaicism and confined placental mosaicism in comparison with postnatally detected mosaicism.

Chromosome	TFM		CPM		PNM	
	Males	Females	Males	Females	Males	Females
1	0	0	0	0	2	0
2	9	5	11	18	3	3
3	2	2	13	11	2	6
4	1	6	0	0	1	0
5	5	2	4	9	0	0
6	2	5	1	6	1	0
7	12 >	3	40 >	24	11 >	4
8	17 >	6	21 >	15	25 >	5
9	11	17	11	17	10	21
10	2 >	1	6 >	5	4 >	3
11	3	0	2	4	0	0
12	2	< 17	8	< 25	4	< 16
13	8	9	17	18	11	24
14	2	< 5	4	< 5	11	< 29
15	2	8	11	16	5	5
16	5	14	25	40	3	3
17	5	6	7	14	5	0
18	8	< 11	21	< 25	10	< 22
19	0	1	0	0	1	0
20	9 >	7	27 >	16	6 >	4
21	9	< 11	13	< 19	12	< 15
22	5	< 10	7	< 18	12	< 19
Total	119	146	249	305	139	179
Sex ratio	0.8		0.8		0.8	

Table 2: Fetal clinical status/pregnancy outcome according to mosaic carriers' gendera

Studied cohort	Males				Females			
	Normal	Abnormal	IUFD	Not stated [b]	Normal	Abnormal	IUFD	Not stated [b]
True fetal mosaicism	45	49	6	16	41	73	5	14
Proportion of abnormal fetuses/ outcomes and IUFD	49/100=49%		6/100=6%		73/119=61%		5/119=4%	
Confined placental mosaicism	150	18	13	51	200	25	12	52
Proportion of abnormal fetuses/ outcomes and IUFD	18/181=10%		13/181=7%			25/237=11%	12/237=5%	
No confirmatory study	33	5	5	14	25	13	17 (2 abn)	14
Proportion of abnormal fetuses/ outcomes and IUFD	5/43=12%		5/43=12%		13/55=24%		17/55=31%	

[a]cases with diagnosed UPD 7, 14, 15, 16 not included; [b]few cases of uncertain clinical significance are allocated to this category

Citation: Natalia V. Kovaleva, Philip D. Cotter. Mosaicism For Autosomal Trisomies: A Review of The Literature Suggests Inverse Effects of Carriers' Gender and Maternal Age on Clinical Manifestations. Obstetrics and Gynecology Research. 7 (2024): 116-128.

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Inconsistencies with these two "mainstreams" of some trisomies (for example, mosT3 and mosT5) may be due to their small sample sizes. Therefore, more cases should be analyzed for final conclusions.

Mosaic carriers' gender and pregnancy outcomes

Pregnancy outcomes, depending the fetus gender, were studied in three cohorts separately: True fetal mosaicism (Supplemental Table S1), Confined placental mosaicism (Supplemental Table S2), and Not confirmed (Supplemental Table S3).

Overall figures in Table 2 demonstrated an apparent predominance of females among abnormal outcomes: 49 males and 73 females (SR=0.67), in contrast to 45 males and 42 females (SR=1.07 which is not different from the population value of 1.05) among normal outcomes. A detailed analysis by chromosomes involved (Supplemental Table S1) showed a prevalence of females over males among abnormal carriers of mosT4, mosT9, mosT18, and mosT22. A male predominance among abnormal outcomes was observed for carriers of mosT2. Since these data are of potential clinical significance, more cases should be studied for a clarification of predictive value of the sex-specific effect on clinical manifestation of mosaicism for some chromosomes. Intrauterine death was reported in 7% of males and in 4% of females.

Analysis of the data from Table 2 showed an overall excess of females among both normal outcomes (150 males/200 females, SR=0.75) and abnormal outcomes (18 males/25 females, SR=0.72) in CPM cohort. A prevalence of females was observed among abnormal carriers of mosT9, mosT11, most 12 and mosT22 (Supplemental Table S2). Intrauterine death was reported in 7% of males and in 4% of females, similar to figures observed in TFM.

Analysis of SR according to reported/deduced CPM levels showed similar figures, SR=0.73 (19 males/26 females) in CPM1 cohort, SR=1.0 (41 males/41 females) in CPM2 cohort, and SR=0.84 (65/77 females) in CPM3 cohort, with no statistically significant difference between them. This is an interesting observation since both CPM1 and CPM2 have been considered to have mostly mitotic origin in contrast to CPM 3 which is considered to have a meiotic origin [15].

Table 2 demonstrated a female predominance not only among abnormal outcomes with an excess of mosT9 (Supplemental Table 3) but also among intrauterine deaths. Overall, there were 33 males/25 females (SR=1.3, not different statistically from the population value of 1.05) among normal outcomes unlike to 5 males/13 females (SR=0.4) among abnormal outcomes, mid-p=0.035. It was previously reported that this group included a large number of fetal loss cases with no further study on the lost fetus (see Materials and Methods). The proportions of fetal losses was different from those in both TFM and CPM cohorts; 12% among male carriers and 31% among female carriers, mid-p=0.021

The data obtained is of significance for genetic counseling of pregnancies with a mosaic fetus. It would be practical to apply a gender-based approach to further studies in this field aiming to get more precise data for better risk estimations.

Pregnancy outcome according to carriers' gender and maternal age in prenatal diagnoses

No difference in maternal ages between prenatally diagnosed male and female mosaic carriers was found, presumably due to general bias to older age, since advanced maternal age (AMA) is one of the most common indications for prenatal testing. However, a more detailed analysis revealed a difference in AMA proportion between both male and female carriers normal and abnormal outcomes in every examined prenatal cohort (Table 3, Supplemental Tables S4-S6).

AMA proportions were 65% vs 55% in TFM cohort (Supplemental Table S4), 73% vs 54% in CPM (Supplemental Table S5), and 88% vs 50% in the Not confirmed cohort (Supplemental Table S6). Overall figures were 75% vs 56%, p=0.0015 [10].

One may conclude a "positive effect" of AMA presumably due to both age-associated selective miscarriage of abnormal fetuses and/or placental incompetence. However, as was stated in our previous review, women with pregnancy loss were younger than mothers of normal offspring and slightly younger than those with abnormal outcome, with average age of 33.3 yr and 50% proportion of AMA [10]. In contrast, female gender appeared to demonstrate an apparent "negative" effect by increasing the risk of fetal abnormality. These contrasting effects on clinical manifestation of mosaic trisomies are intriguing and deserve further careful studies.

Sex ratio and intrauterine growth restriction

It should be noted that in the previous article based on the same data collection [10], maternal age distributions did not differ between IUGR cases and those with normal birth weight (appropriate to gestational age). Among the TFM cohort, a small number cases of isolated IUGR were reported, with a male prevalence, SR=2.5 while among CPM cohort, we observed a female prevalence, SR=0.6 (Table 4). There is no correlation between chromosome-specific rates of IUGR with the number of studied CPM cases. For example, among 64 cases of mosT7 only three IUGR cases were reported (1 in 21), in contrast to cases of mosT8, with 10 IUGR among 36 CPM cases (1 in 4). It was stated that increased risk for IUGR in CPM is correlated with meiotic origin of trisomy [15], however, mosT8 is mostly of mitotic origin [16]. A high rate of IUGR observed among mos16 cases (1 in 4), is in accordance with their mostly meiotic origin.

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Table 3: Proportion of mothers of advanced age according to fetal clinical status/pregnancy outcome and mosaic carriers' gender [a]

Studied cohort	Males		Females		Total	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
True fetal mosaicism	37	34	38	62	75	96
Proportion of AMA	59%	41%	71%	63%	65%	55%
Confined placental mosaicism	74	14	107	21	181	35
Proportion of AMA	72%	36%	74%	67%	73%	54%
No confirmatory study	13	4	4	8	17	12
Proportion of AMA	92%	75	75	38%	88%	50%

[a] cases with diagnosed UPD 7, 14, 15, 16 not included

Table 4: Intrauterine growth restriction in TFM and CPM, distribution by chromosome and gender.

Chromosome		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20	21	22	Total	SR
TFM	Males	2	1	0	0	0	2	0	2	0	0	0	1	0	0	1	0	0	0	1	0	10	2.5
	Females	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	1	4	
CPM	Males	1	1	0	0	0	2	3	1	0	0	0	2	0	0	9	0	2	0	1	1	23	0.6
	Females	5	1	0	2	3	1	7	1	0	0	1	1	3	1	6	1	1	0	1	4	39	

Inkster et al. [17] stated that female fetuses were reported to be at an increased risk of IUGR for decades. This the true for the CPM group as a whole, with 23 males/39 females, SR=0.6. However, there are some intriguing findings, i.e. opposite SR in mosT8 and mosT16.

MosT8 is characterized by apparent male predominance through TFM with SR=2.8, CPM with SR=1.4, and PNM with SR=5.0 (see Table 1), but not in IUGR cases, with 3 males/7 females, SR=0.4. MosT16 demonstrated a strong female predominance through TFM with SR=0.4 and CPM with SR=0.6 (Table 1), but not among IUGR cases, with 9 males/6 females, SR=1.5. Further gender-oriented studies will clarify the nature of these findings.

Maternal age and mosaic carriers gender in postnatal diagnoses

Maternal age distributions were slightly different between male and female patients (Table 5). Firstly, mothers of male carriers were younger compared to mothers of female carriers, with AMA proportion of 23% compared to AMA proportion of 33%. Secondly, for males' maternal age we observe apparent single-vertex distribution with the only peak in 30-34 yr group. For females' maternal age, the distribution looks like bimodal with peaks in 25-29 yr and in 35-39 yr groups suggestive the existence of two subpopulations, age-independent and age-dependent.

Maternal ages of cases with familial mosaicism, at birth of the first mosaic child, were excluded but marked with an asterisk. It is notable that a higher prevalence of mothers was diagnosed to be mosaics in the female group (1 in 24) compared to the male group (1 in 90). Familial transmission of mosaicism is not an infrequent (though enigmatic) phenomenon, it is age-independent, typically inherited from maternal side, and likely to be diagnosed predominantly in female probands [18]. Therefore a question arises, if the same chromosome is lost preferably in both mosaic mothers and their mosaic offspring?

Sex ratios in nonmosaic and mosaic trisomies in spontaneous abortions

Variations in the sex ratio among carriers of mosaic trisomies are discussed frequently as fetuses intolerance to one or another trisomy [7,16,19]. Therefore, it was appropriate to study parameters of interest in spontaneous abortuses (Table 6) [20-57].

Sex ratios among most common nonmosaic trisomies varies significantly, from 1.4 (T13 and T21) to 0.8 (T15) with the overall figure of 1.07. However SR of their mosaic form may be very different, tending to be female-biased, with the overall figure of 0.94. Among nonmosaic trisomies, 12 of 22 autosomes demonstrated a slight (T4, T8, T18) to strong male predominance (T13, T21) while among mosaic trisomies, there are only three of them (mosT2, mosT16, and mosT18) presenting with male predominance.

It is unclear why a strong selection occurs against males with mosT16 (SR=2.25), but not against nonmosaic

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Table 5: Maternal age of mosaic carriers diagnosed postnatally.

Maternal age	Males	Females	Total
<20	5*	2 **	7
20-24	18	22 **	40
25-29	18	33 *	51
30-34	26	19	45
young	2	4	6
35-39	14	24	38
40-44	4	14	18
45+	2	0	2
AMA	1	1	2
Total	90	119	209
Proportion of AMA	21/90=23%	39/119=33%	60/209=29%

* Mosaic mother, age at birth of first mosaic child, not included.

Table 6: Cytogenetic profiles and sex ratios in regular and mosaic trisomies in spontaneous abortions (data collated from 38 published reports)

Chromosome	Nonmosaic trisomies				Mosaic trisomies		
	Males	Females	Sex not stated	Total	Males	Females	Total
1	1	1	0	2	0	0	0
2	21	27	11	59	5	3	8
3	6	6	7	19	2	3	5
4	22	18	12	52	1	3	4
5	5	2	0	7	1	2	3
6	9	6	6	21	0	0	0
7	25	27	11	63	3	3	6
8	22	20	16	58	1	1	2
9	12	31	15	58	2	2	4
10	16	17	7	40	1	1	2
11	4	6	0	10	0	0	0
12	10	11	2	23	0	2	2
13	64	45	29	138	2	4	6
14	27	33	16	76	2	1	3
15	59	72	44	175	2	5	7
16	228	209	124	561	18	8	26
17	5	3	25	33	0	0	0
18	39	34	32	105	3	1	4
19	2	1	0	3	1	0	1
20	16	18	8	42	0	3	3
21	122	90	45	257	1	3	4
22	109	94	68	271	4	7	11
Total	824	772	478	2073	49	52	101
Sex ratio	1.07				0.94		

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

T16 (SR=1.1). However, this finding is consistent with the suggestion of Young et al. [6] that an excess of females among carriers of mosT16 prenatal diagnoses may be explained by selection against male mosaic trisomy 16 embryos.

In summary, the analysis of SR in aborted carriers of mosaic trisomies gives no universal key to understanding SR in both prenatal and postnatal diagnosis, not only because of apparently small sample sizes for the majority of nonmosaic and of mosaic forms particularly. It might be more practical to consider data from the assisted reproduction field, but unfortunately we did not identify publications reporting gender of the studied embryos, either with nonmosaic or mosaic trisomies.

In contrary to our previous study of the same dataset [10], the majority of differences indicated did not reach statistical significance due to splitting studied cohorts by gender resulting in reducing sample sizes. For example, an apparent difference between 45 males/42 females among normal outcomes vs 49 males/73 females among abnormal outcomes (Table 2).does not reach minimal statistical significance. In this case, under desired power 0.80 and significance level $\alpha = 0.05$, required sample sizes should be 242 males and 315 females. Thus, this study, despite of analyzed literature magnitude, looks like 'observational' and requires further strengthening which can be achieved only by collective international efforts.

Conclusions

Current study is the first one aimed to consider diverse aspects of sex ratio variations in somatic diploid/trisomic mosaicism. Based on our previous experience, analysis of SR variations may be considered an effective tool for recognition and examination of diverse pathological processes, and risks prediction. Therefore we opted to apply this tool to this long-term extensively studied field.

Despite of apparent limitations due to inevitable consequence of splitting of examined cohorts by gender, SR-based analysis has brought interesting and potentially practical results including a sex-specific negative effect of certain chromosomes involved and negative effect of female gender opposite to positive effect of advanced maternal age. Considering the results reporting in this paper to be preliminary, we accentuate the need of further gender-based data collecting, aiming to get the most accurate risk estimations.

Acknowledgments

The authors are greatly indebted to Nikita N. Khromov-Borisov for the statistical analysis of the data

Conflicts of Interest

P.D.C. was employed by the company ResearchDx. N.V.K. declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Chitham RG, Maciver EA Cytogenetic And Statistical Survey Of 105 Cases Of Mongolism. Ann Hum Genet 28 (1965): 309-315.
2. Magenis RE, Hecht F, Milham S Jr. Trisomy 13 (D1) syndrome: studies on parental age, sex ratio, and survival. J Pediatr 73 (1968): 222-228.
3. Le Marec BM, Lair JC, Kérisit J, et al. A propos de 20 cas de trisomie 18. Considérations sur le sex-ratio en fonction de l'age maternel [20 cases of trisomy 18. Sex-ratio in relation to age of the mother]. Ann Pediatr (Paris) 24 (1977): 125-136.
4. Alberman E, Mutton D, Morris JK. Cytological and epidemiological findings in trisomies 13, 18, and 21: England and Wales 2004-2009. Am J Med Genet A 158A (2012): 1145-1150.
5. Nikitina TV, Sazhenova EA, Zhigalina DI, et al. Karyotype evaluation of repeated abortions in primary and secondary recurrent pregnancy loss. J Assist Reprod Genet 37 (2020): 517-525.
6. Yong PJ, Barrett IJ, Kalousek DK, et al. Clinical aspects, prenatal diagnosis, and pathogenesis of trisomy 16 mosaicism. J Med Genet 40 (2003): 175-182.
7. Thomsen SH, Lund ICB, Fagerberg C, et al. Trisomy 8 mosaicism in the placenta: A Danish cohort study of 37 cases and a literature review. Prenat Diagn 41 (2021): 409-421.
8. Morris JK, Savva GM. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. Am J Med Genet A 146A (2008): 827-832.
9. Kovaleva NV, Cotter PD. Factors affecting clinical manifestation of chromosomal imbalance in carriers of segmental autosomal mosaicism: differential impact of gender. J Appl Genet 63 (2022): 281-291.
10. Kovaleva NV, Cotter PD. Mosaicism for Autosomal Trisomies: A Comprehensive Analysis of 1266 Published Cases Focusing On Maternal Age and Reproductive History. Genes 15 (2024): 778.
11. Liehr T. ChromosOmics UPD Database, https://cs-tl.de/DB/CA/UPD/0-Start.html
12. Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. Hum Mol Genet 16 Spec No. 2 (2007): R203-208.
13. Benn P. Trisomy 16 and trisomy 16 Mosaicism: a review. Am J Med Genet 79 (1998): 121-133.

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

14. Kovaleva NV. Sex-specific chromosome instability in early human development. Am J Med Genet A 136A (2005): 401-413.

15. Robinson WP, Barrett IJ, Bernard L, et al. Meiotic origin of trisomy in confined placental mosaicism is correlated with presence of fetal uniparental disomy, high levels of trisomy in trophoblast, and increased risk of fetal intrauterine growth restriction. Am J Hum Genet 60 (1997): 917-927.

16. Karadima G, Bugge M, Nicolaidis P, et al. Origin of nondisjunction in trisomy 8 and trisomy 8 mosaicism. Eur J Hum Genet 6 (1998): 432-438.

17. Inkster AM, Fernández-Boyano I, Robinson WP. Sex Differences Are Here to Stay: Relevance to Prenatal Care. J Clin Med 10 (2021): 3000.

18. Kovaleva NV. Germ-line transmission of trisomy 21: Data from 80 families suggest an implication of grandmaternal age and a high frequency of female-specific trisomy rescue. Mol Cytogenet 3 (2010): 7.

19. Chen CP. Prenatal diagnosis and genetic counseling for mosaic trisomy 13. Taiwan J Obstet Gynecol 49 (2010): 13-22.

20. Babu R, Van Dyke DL, Bhattacharya S, et al. A rapid and reliable chromosome analysis method for products of conception using interphase nuclei. Mol Genet Genomic Med (2018): 1–12.

21. Boué J., Daketse M., Deluchst C., et al. Identification par les bandes Q et G des anomalies chromosomiques dans les avortements spontanés // Ann. Genet. 1976. V. 19. P. 233-239.

22. Bruno D.G., Burgess T., Ren H., et al. High-throuput analysis of chromosome abnormality in spontaneous miscarriage using an MLPA subtelomere assay with an ancillary FISH tests for polyploidy // Am. J. Med. Genet. 2006. V. 140A. P. 2786-2793.

23. Byrne J, Warburton D, Kline J, et al. Morphology of early fetal deaths and their chromosomal characteristics. Teratology 32 (1985): 297-315.

24. Carr DH, Gedeon MM. Q-banding of chromosomes in human spontaneous abortions. Can J Genet Cytol 20 (1978): 415-425.

25. Causio F., Rischetto R., Sarcina E., et al. Chromosome analysis of spontaneous abortions after in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) // Eur. J. Obstet. Gynecol. Reprod. Biol. (2002). V. 105. P. 44-48.

26. Cheng HH, Ou CY, Tsai CC, et al. Chromosome distribution of early miscarriages with present or absent embryos: female predominance. J Assist Reprod Genet 31 (2014): 1059-1064.

27. Dória S, Carvalho F, Ramalho C, et al. An efficient protocol for the detection of chromosomal abnormalities in spontaneous miscarriages or foetal deaths. Eur J Obstet Gynecol Reprod Biol 147 (2009): 144-150.

28. Fritz B, Hallermann C, Olert J, et al. Cytogenetic analyses of culture failures by comparative genomic hybridisation (CGH)-Re-evaluation of chromosome aberration rates in early spontaneous abortions. Eur J Hum Genet 9 (2001): 539-547.

29. Gao J, Liu C, Yao F, et al. Array-based comparative genomic hybridization is more informative than conventional karyotyping and fluorescence in situ hybridization in the analysis of first-trimester spontaneous abortion. Mol Cytogenet 5 (2012): 33.

30. Gimovsky AC, Pham A, Moreno SC, et al. Genetic abnormalities seen on CVS in early pregnancy failure. J Matern Fetal Neonatal Med 33 (2020): 2142-2147.

31. Guerneri S., Bettio D., Simoni G., et al. Prevalence and distribution of chromosome abnormalities in a sample of first trimester internal abortions // Hum. Reprod. (1987). V. 2. P. 735-739.

32. Hassold T., Chen N., Funkhouser J., et al. A cytogenetic study of 1000 spontaneous abortions // Ann. Hum. Genet. (1980). V. 44. P. 151-178.

33. Hassold T. Mosaic trisomies in human spontaneous abortions. Hum Genet 61 (1982):31-35. Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. Hum Mol Genet 16 Spec No. 2 (2007): R203-208.

34. Horiuchi I, Wakimoto Y, Kuwata T, et al. Cytogenetic analysis of spontaneous miscarriages using long-term culturing of chorionic villi. J. Fetal Med (2019).

35. Jenderny J. Chromosome aberrations in a large series of spontaneous miscarriages in the German population and review of the literature. Mol Cytogenet 7 (2014): 38.

36. Kajii T., Ferrier A., Niikawa N., et al. Anatomic and chromosomal anomalies in 639 spontaneous abortuses // Hum. Genet. (1980). V. 55. P. 87-92.

37. Karaoguz M.Y., T. Nas, E. Konac, et al. Menevse Is cytogenetic diagnosis of 46, XX karyotype spontaneous abortione specimens erroneous? Fluorescence in situ hybridization as a confirmatory technique J. Obstet. Gynaecol. Res., 31 (2005), pp. 508-513

38. Lin C.C., De Braekeleer M., Jamro H. Cytogenetic studies in spontaneous abortion: the Calgary experience // Can. J. Genet. Cytol. (1985). V. 27. P. 565-570.

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

39. Ljunger E., Cnattingius S., Lundin C., et al. Chromosomal anomalies in first-trimester miscarriages // Acta Obstet. Gynecol. Scand V. 84 (2005). P. 1103-1107.

40. Ma S., Philipp T., Zhao Y., et al. Frequency of chromosomal abnormalities in spontaneous abortions derived from intracytoplasmic sperm injection compared with those from in vitro fertilization // Fertil. Steril V. 85 (2006). P. 236-239.

41. Meulenbroek GH, Geraedts JP. Parental origin of chromosome abnormalities in spontaneous abortions. Hum Genet 62 (1982): 129-133.

42. Miskovic S, Culic V, Konjevoda P, et al. Positive reproductive family history for spontaneous abortion: predictor for recurrent miscarriage in young couples. Eur J Obstet Gynecol Reprod Biol 161 (2012): 182-186.

43. Nagaishi M, Yamamoto T, Iinuma K, et al. Chromosome abnormalities identified in 347 spontaneous abortions collected in Japan. J Obstet Gynaecol Res 30 (2004): 237-241.

44. Nikitina TV, Sazhenova EA, Zhigalina DI, et al. Karyotype evaluation of repeated abortions in primary and secondary recurrent pregnancy loss. J Assist Reprod Genet 37 (2020): 517-525.

45. Ocak Z, Özlü T, Ozyurt O. Association of recurrent pregnancy loss with chromosomal abnormalities and hereditary thrombophilias. African Health Sciences 2013; 13 (2013): 447-452.

46. Ohno M., Maeda T., Matsunobu A. A cytogenetic study of spontaneous abortions with direct analysis of chorionic villi // Obstet. Gynecol V. 77. (1991) P. 394-398.

47. Qumsiyeh MB. Chromosome abnormalities in the placenta and spontaneous abortions. J Matern Fetal Med 7 (1998): 210-212.

48. Robberecht c., Schuddinck V., Fryns J.P., et al. Diagnosis of miscarriages by molecular karyotyping: benefits and pitfalls // Genet. Med. V. 11. (2009) P. 646-654.

49. Robinson W P, McFadden D E, Stephenson M D. The origin of abnormalities in recurrent aneuploidy/ polyploidy. Am J Hum Genet 69 (2001): 1245-1254.

50. Schaeffer A.J., Chung J., Heretis K., et al. Comparative genomic hybridization- array analysis enhances the detection of aneuploidies and submicroscopic imbalances in spontaneous miscarriages // Am. J. Hum. Genet V. 74. (2004) P. 1168-1174.

51. Schilit SLP, Studwell C, Flatley P, et al. Chromosomal microarray analysis in pregnancy loss: Is it time for a consensus approach? Prenat Diagn 42 (2022): 1545-1553.

52. Silvestre E, Cusí V, Borrás M, et al. Cytogenetic and morphologic findings in chorionic villi from spontaneous abortions. Birth Defects Orig Artic Ser 30 (1996): 353-357.

53. Songster GS, Sun L, Chang SC, et al. Chromosome analysis in spontaneous pregnancy loss: use of placental villus mesodermal core cell cultures. Am J Med Genet 42 (1992): 785-788.

54. Strom C.M., Ginsberg N., Applebaum M. Analysis of 95 first-trimester spontaneous abortions by chorionic villus sampling and karyotype // J. Assist Reprod. Genet V. 9. (1992) P. 458-461.

55. Tavokina LV, Sopko NI, Khazhilenko KG, et al. [Molecular-cytogenetic study of the aborted fetuses in women with reproductive function disorders]. Tsitol Genet 40 (2006): 72-78.

56. Warburton D, Yu CY, Kline J, et al. Mosaic autosomal trisomy in cultures from spontaneous abortions. Am J Hum Genet 30 (1978): 609-617.

57. Xu J, Chen M, Liu QY, et al. Detecting trisomy in products of conception from first-trimester spontaneous miscarriages by next-generation sequencing (NGS). Medicine (Baltimore) 99 (2020): e18731.

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

SUPPLEMENTARY FILES

Supplementary Table S1. True fetal mosaicism: normal and abnormal fetuses/outcomes according to mosaic carriers gender [a]

Chromosome	Males, n=116				Females, n=133			
	Normal	Abnormal	Intrauterine fetal death	Not stated [b]	Normal	Abnormal	Intrauterine fetal death	Not stated [b]
1	0	0	0	0	0	0	0	0
2	3	6	0	0	1	3	1	0
3	1	1	0	0	2	0	0	0
4	1	0	0	0	0	6	0	0
5	2	3	0	0	0	2	0	0
6	0	1	1	0	1	4	0	0
7	5	3	0	2	0	0	1	1
8	8	4	1	4 (1 minor heart defect)	4	1	0	1
9	6	5	0	0	2	13	0	2 (1 minor DF of uncertain significance)
10	0	2	0	0	0	1	0	0
11	1	1	1	0	0	0	0	0
12	1	1	0	0	11	6	0	0
13	4	2	2	0	4	1	0	4 (1 low set ears)
14	0	0	0	1	1	3	0	0
15	1	1	0	0	0	2	0	2
16	2	2	0	0	1	**9**	0	1
17	0	4	0	1	2	4	0	0
18	2	3	0	3	2	5	2	2
19	0	0	0	1	0	0	0	0
20	4	4	0	1 slight facial dysmorphia	3	4	0	0
21	4	2	0	3	5	3	0	3
22	0	4	1	0	2	6	1	1 neonatal death
Total	45	49	6	16	41	73	5	14
Proportion of abnormal fetuses/outcomes		49/100=49%	7/100=7%			73/119=61%	5/119=4%	
*cases with diagnosed UPD 7, 14, 15, 16 not included								
[b] few cases of uncertain clinical significance are allocated to this category								

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Supplementary Table S2: Confined placental mosaicism: normal and abnormal fetuses/outcomes according to gender [a]

Chromosome	Males, n=232				Females, n=289			
	Normal	Abnormal	Intrauterine fetal death	Not stated [b]	Normal	Abnormal	Intrauterine fetal death	Not stated [b]
2	7	4	0	0	13	3	1	1
3	11	1	0	1	9	0	1	1
4	0	0	0	0	0	0	0	0
5	4	0	0	0	8	1	0	0
6	1	0	0	0	6	0	0	0
7	22	1	2	13	18	0	1	5
8	11	0	0	10	7	0	0	8
9	5	0	2	4	11	3	0	3
10	5	0	1	0	3	0	1	2
11	2	0	0	0	4	0	0	0
12	7	0	0	1	19	4	0	2
13	13	1	2	1	13	0	1	4
14	2	0	0	1	3	0	0	5
15	5	0	0	0	9	1	2	0
16	9	4	1	4	13	**4**	4	6
17	6	1	0	0	14	0	0	0
18	15	1	1	4	16	0	0	6
20	19	1	1	5	11	3	0	2
21	4	2	2	5	14	1	0	4
22	2	2	1	2	9	5	1	3
Total	150	18	13	51	200	25	12	52
Proportion of abnormal fetuses/ outcomes		18/181=10%	13/181=7%			25/237=11%	12/237=5%	

[a] cases with diagnosed UPD 7, 14, 15, 16 not included; [b] few cases of uncertain clinical significance are allocated to this category

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Supplementary Table S3. No confirmatory study or data not available: normal and abnormal fetuses/outcomes according to gender [a]

Chromosome	Males, n=57				Females, n=69			
	Normal	Abnormal	Intrauterine fetal death	Not stated [b]	Normal	Abnormal	Intrauterine fetal death	Not stated [b]
2	4	1	1	0	4	1	4	2
3	4	0	0	2	0	0	0	1
4	2	0	0	0	1	0	1	0
5	0	0	0	0	1	0	0	0
6	0	0	0	0	1	0	0	0
7	1	0	0	3	6	0	0	0
8	0	0	0	0	4	1	0	0
9	2	1	1	0	0	7	1	0
10	0	0	0	0	0	0	1 (abn)	1
11	1	0	0	0	0	0	0	1
12	3	0	0	0	0	1	2	0
13	1	0	1	1	0	0	0	0
14	0	2	0	0	0	2	0	0
15	2	0	0	0	0	0	0	1
16	0	0	0	2	**2**	0	3	2
17	3	0	0	0	3	1	1 (abn)	0
18	2	1	1	0	2	0	2	1
19	0	0	0	0	0	0	0	0
20	6	0	0	2	0	0	0	0
21	0	0	1	4	1	0	0	5
22	2	0	0	0	0	0	2	0
Total	33	5	5	14	25	13	17	14
Proportion of abnormal fetuses/ outcomes		5/43=12%	5/43=12%			13/55=24%	17/55=31%	

[a] cases with diagnosed UPD 7, 14, 15, 16 not included;

Kovaleva NV and Cotter PD., Obstet Gynecol Res 2024
DOI:10.26502/ogr0170

Supplementary Table S5. Gender and clinical status of mosaic carriers in CPM cohort according to maternal ages [a]

Maternal age	Males		Females		Total	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
<20	1	0	1	0	2	0
20-24	0	4	4	1	4	5
25-29	5	3	8	2	13	5
30-34	15	2	15	4	30	6
35-39	34	4	56	5	90	9
40+	13	1	15	7	28	8
AMA	6	0	8	2	14	2
Total	74	14	107	21	181	35
Proportion of AMA	72%	36%	74%	67%	73%	54%

[a] cases with diagnosed UPD 7,14,15,16 not included

Supplementary Table S6. Gender and clinical status of mosaic carriers in Not confirmed cohort according to maternal ages [a]

Maternal age	**Males**		**Females**		**Total**	
	Normal	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**
<20	0	0	0	0	0	0
20-24	1	0	0	1	1	1
25-29	0	1	1	2	1	3
30-34	0	0	0	2	0	2
35-39	6	3	1	3	7	6
40-44	6	0	2	0	8	0
Total	13	4	4	8	17	12
Proportion of AMA	12/13=92%	3/4=75%	3/4=75%	3/8=38%	15/17=88%	6/12=50%

[a] cases with diagnosed UPD 7,14,15,16 not included