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## Full trisomy 5 in a sample of spontaneous abortion and arias stella reaction

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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### Summary

- Background:** Historically, 50% of spontaneously expelled abortuses have been thought to be chromosomally abnormal; about 60% are trisomies. In general, trisomy 16 is the most frequent chromosomal abnormality, followed by trisomy 21 and trisomy 22. So far only 1 case of a female fetus with multiple congenital malformations associated with full trisomy 5 has been described.
- Case Report:** We present a case of *de novo* full trisomy 5 in a spontaneous abortion sample. A young couple with normal constitutional karyotype experienced the second spontaneous abortion at 9 weeks of gestation, with the cytogenetic formula 47,XX,+5 in all analyzed cells.
- Conclusions:** The routine cytogenetic analysis of miscarriages is still an uncommon practice, but it can have a great impact on the management of couples with repeated pregnancy wastage. Besides of the obvious cost benefit for health care, such analysis would help the physician to decide about future patient management, as well as planning the genetic counseling.
- key words:** trisomy 5 • spontaneous abortion • arias stella reaction

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## BACKGROUND

Spontaneous abortion is a common clinical problem that occurs in 10–15% of all clinically recognized pregnancies. Historically, 50% of spontaneously expelled abortuses have been thought to be chromosomally abnormal. The majority (95%) of chromosomal anomalies are numerical. About 60% are trisomies, 20% are monosomies, and 15% have ploidy, especially triploidy. Most of these terminate *in utero*, making the extra or missing chromosome status the leading known cause of miscarriage [1]. In the case of a numerical chromosomal anomaly in spontaneous abortion, parental chromosomes are usually normal [2].

Most aneuploidy derives from errors in maternal meiosis I, usually producing autosomal trisomies.

Maternal age is a great risk factor for most human trisomies and consequent miscarriage. Its incidence rises from 15% in women under 25 years of age to 35% after age 38. There is limited epidemiological evidence for a paternal age effect, which is more likely to involve meiotic II errors of the sex chromosomes. However, it has recently been shown that there is a correlation between age and increase in sperm aneuploidy. Although rare, paternally derived trisomy tends to abort earlier [2].

These and other differences suggest that constitutional aneuploidy arises by multiple mechanisms [3].

In general, trisomy 16 is the most frequent chromosomal abnormality, and accounts for approximately a third of chromosomal abnormalities in early pregnancy [4].

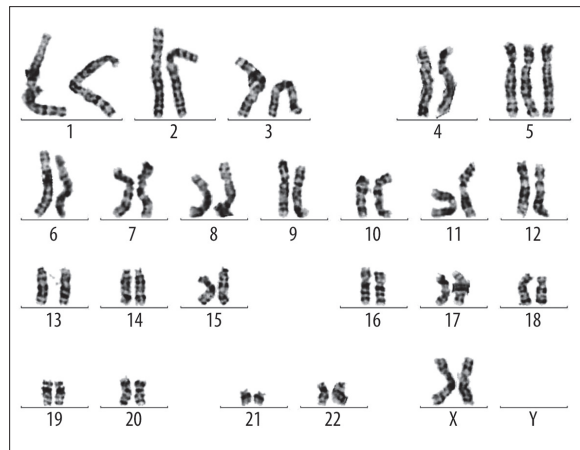
Several cases (in a clinically recognized pregnancy) of trisomy 5 in aborted material have been reported. However, despite of the molecular cytogenetic techniques used for aneuploidy detection, trisomy 5 in aborted material has been observed only in sporadic cases [5–8].

Even by using comparative genomic hybridization (CGH) technique, trisomy 5 was found in only 1 first trimester missed abortion [9]. In all other CGH/spontaneous abortion studies no trisomy 5 was observed [10–12].

## CASE REPORT

We present here a case of a rare type of mutation – single trisomy 5 in spontaneous abortion sample. Cells (fibroblasts) isolated from product of conception were cultured, and cytogenetic analysis by G-banding showed 47,XX,+5 [7] karyotype (Figure 1). A young childless couple (a 27-year-old woman and a 30-year-old man) with normal constitutional karyotype (46,XX and 46,XY) visited Clinical Hospital Split, Croatia after the woman experienced her second spontaneous abortion. The first spontaneous abortion was a year before. It was not cytogenetically analyzed; clinically it was diagnosed as a missed abortion at 8 weeks of gestation. Pathohistological analysis revealed extensive Arias Stella reaction in endometrial glands and partially degenerative and mildly hydropic chorionic villi, most of them avascular or with faintly visible remnants of former fetal vessels [13].

The second spontaneous abortion was at 9 weeks of gestation, with the cytogenetic formula 47,XX,+5 [7]. Pathohistology



**Figure 1.** Karyotype: 47,XX,+5[7] from spontaneous abortion material.

revealed the same Arias Stella reaction, with mesenchymal and immature intermediate well vascularized villi. In the family history, the wife's sister had 2 spontaneous abortions at the same gestational period, while the husband's mother had 1 spontaneous abortion.

The research conformed to the Helsinki Declaration and to the Ethics Committee, Clinical Center Split. All patients' samples and clinical details were obtained upon receiving patients' consent and the Ethics Committee approval.

During normal pregnancy, to prevent bleeding, the concentrations of inhibitors of fibrinolysis and the concentration of many clotting factors rise to achieve a precise balance between hypofibrinolysis and hypercoagulation. Therefore, the coordinated expression of all of these factors plays a fundamental role in maintaining normal pregnancy. However, coagulation homeostasis defects (thrombotic, hypercoagulable) are quite common during pregnancy, leading to fetal wastage due to thrombosis of early placental vessels [14–16]. As certain polymorphisms in some maternal thrombophilia genes are associated with pronounced thrombotic defects [17–20] we additionally tested mother's blood sample for the presence of specific polymorphisms in genes *ACE*, *PAI-1*, *MTHFR*, *FVL* and *FII*.

The *ACE* gene product, angiotensin-I converting enzyme, has a physiological function in the fibrinolysis pathway. The enzyme converts angiotensin I to angiotensin II, which is very important in regulation of fetoplacental complex functions. This regulation is mainly attributed to the insertion/deletion (I/D) of a 287 bp Alu-repeat polymorphism in intron 16 of the *ACE* gene, the so-called *ACE* I/D polymorphism. The presence of the D/D alleles correlates with increase of *ACE* concentration in blood and subsequently with the increase of *PAI-1* expression, resulting in reduced fibrinolysis. This polymorphism was recently found to be associated with spontaneous abortion [17,18,21]. *PAI-1* (plasminogen activator inhibitor-1) is a key regulating element in the fibrinolysis cascade, whose expression is influenced by angiotensin II plasma level, as well as 4G/5G polymorphism in the *PAI-1* promoter, at the position -675. Comparable to *ACE* D/D alleles, 4G/4G alleles potentiate expression of the *PAI-1* gene, leading to reduction of fibrinolysis [22].

The relationship between the *MTHFR* (methylene tetrahydrofolate reductase) gene mutation and spontaneous abortion is still not clear. The gene codes for the enzyme that catalyses the reduction of 5',10-methylene tetrahydrofolate to a predominant circulating form of folate, which allows re-methylation of homocystein in methionine. However, it has been reported that nucleotide change (polymorphism) at the position 667 (C667T) results in an alanine to valine substitution (codon 225, predicted catalytic domain of *MTHFR*) and lowers enzyme activity, leading to the hyperhomocysteinemia and elevated risk of spontaneous abortion [19,23].

Coagulation factor V Leiden (*FVL*) and factor II (*FII*, prothrombin) gene mutations are the most common causes of thrombophilia and placental dysfunction. *FVL* gene mutation (Arg<sub>506</sub>→Gln substitution at nucleotide position 1691) causes resistance to activated protein C (APC). This resistance is the most common cause of thrombosis [20]. Mutation in *FII* gene (G20210A substitution in the 3' untranslated region) leads to elevated blood prothrombin level, which in turn causes increased risk for thrombosis and spontaneous abortion [24,25].

Only *ACE* gene analyzed in mothers' blood lymphocytes exhibited polymorphism (homozygosity for D allele, DD 190 bp) associated with an elevated risk for spontaneous abortion due to the elevated PAI-I concentration and reduced fibrinolysis [17,18,21]. Genotypes of all other genes tested did not show any harmful polymorphism.

## DISCUSSION

As mentioned earlier, only a few cases of trisomic fetuses have been described. By using conventional and trypsin G-staining and by DNA typing using highly polymorphic microsatellite markers, trisomy 5 in spontaneous abortion material was recorded in a total of 6 cases [5–8]. Comparative genomic hybridization, a powerful new molecular cytogenetic technique, has been used for chromosome analysis in spontaneous abortions in only a limited number of studies [10–12]; however, trisomy 5 was recorded in only 1 first trimester missed abortion [9]. Even combined QF-PCR and MALPA molecular analysis of total 1539 miscarriage products did not reveal any trisomy 5 cases [26].

However, when double aneuploidy, which is a relatively rare phenomenon, is concerned, 7 more cases of chromosome 5 trisomy were described. The double trisomies 5/8 were observed in 3 cases [27,28] and double trisomies 5/2, 5/7, 5/12 and 5/16 in single cases [28–31].

In addition to the maternal-age effect mentioned earlier, trisomy occurrence depends also on chromosome structure, including very small effects for the large chromosomes (groups A and B), increased effect on chromosome 16, and exponentially increased effect on chromosome 21. This may explain why trisomy 5 is a rare event.

Little is known about the possible phenotype of trisomic spontaneous abortions. In a study correlating parental origin of trisomy with phenotype, Zaragozza et al. [32] found no difference in the proportion of cases with trophoblastic hyperplasia, fetal tissue, nucleated red blood cells, or hydropic villi among paternally or maternally derived trisomies 2, 7, 15, or 22.

In the case of the young couple described in this paper, Arias-Stella reaction was indicated in both cases of miscarriage. This glandular change is a physiologic response to the presence of chorionic tissue and is probably not directly related to trisomy 5.

## CONCLUSIONS

For still unknown reasons, abortion due to the aneuploidy occurs frequently in people with normal constitutional karyotype. However, the routine cytogenetic analysis of miscarriages is still an uncommon practice that has a great impact on the management of couples with repeated pregnancy wastage. In addition to the obvious cost benefit for health care, such analysis would help the physician to decide about future patient management as well as planning genetic counseling, considering that miscarriage can have a deep emotional and psychological effect on both partners.

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