INCIDENCE OF PRENATAL PERICENTRIC INVERSION OF CHROMOSOME 9 IN POPULATION OF WESTERN SERBIA

Ana Milosevic-Djeric[1] PhD; Milena Acimovic[1] PhD; Gordana Sosic[2] M.sc;Tanja Novakovic[2] M.sc.
[1]Department of Gynaecology and Obstetrics, Hospital Centre Uzice, Uzice, Serbia, ana.mdjeric@gmail.com
[2]Clinic of Gynaecology and Obstetrics, Clinics Centre Kragujevac, Kragujevac, Serbia

Abstract: *The pericentric inversion of chromosome 9 is the most common heteromorphism in the general population with frequency 1-3%. The aim of our study was to determine incidence of prenatal pericentric inversion of chromosome 9 in western region of Serbia and to assess the perinatal outcomes of such fetuses. We investigated 949 fetus karyotypes from amniotic fluids. Results revealed that pericentric inversion of chromosome 9 (p11;q12)/(p11;q13) is the most common structural chromosome aberration. Inversion was found in 24 cases with incidence of 2,5 %. The frequency of the pericentric inversion of chromosome 9 in prenatal samples of population in western Serbia is in accordance with the expected incidence in the human population. Our data support the clinical reports that inversion of chromosome 9 is associated with a normal outcome.*

Keywords: *inversion, chromosome 9, incidence*

1. INTRODUCTION

Inversions are balanced structural rearrangement occurs when a segment of a chromosome breaks off and then rearrange. Inversions usually do not involve a loss of genetic information, but simply rearranges the linear gene sequence on chromosome. The inversion may involve centromere when there is is a break in each arm of the chromosome then is called a pericentric inversion. When the inversion involves just one arm of the chromosome, it is called a paracentric inversion.

Pericentric inversions of chromosome 9 are the most common type of small structural inversion seen in humans chromosomes. The two most common inversions are inv(9)(p11q12) and inv(9)(p11q13) [1]. Chromosome 9 displays the highest degree of structural variability in humans. The incidence of pericentric inversions of chromosome 9 is found to be about 1% to 3% in the general population.

The reorientation of genetic material on chromosome usually does not influence on its function. Pericentric inversion of chromosome 9 is usually balanced rearrangement with no extra or missing DNA and does not have phenotypic effect in the majority of cases. Heterozygote carriers of the pericentric chromosome 9 inversion are at high risk of producing abnormal gametes during meiosis that may lead to unbalanced offspring. During meiosis I, a loop will be formed in chromosome with inversion which can lead to produce a percentage of abnormal and unbalanced gametes. These gametes may show duplication of the region outside the inversion segment on one arm of the inverted chromosome and deletion of the terminal segment on the other arm and vice versa, ending up with recombinant chromosomes with partial monosomy or partial trisomy [2].

Inversion of chromosome 9 is generally considered as a as a minor chromosomal rearrangement which does not correlate with abnormal phenotypes. Although it has also been reported in the literature that it is sometimes associated with increased congenital abnormalities (3, 4), growth defect (5), acute leukemia (6), ovarian cancer (7), and schizophrenia. Many reports raised the association of these inversions with infertility, recurrent abortions (8, 9).

Šípek *et al*. have published the largest study on inv(9) and have found a higher frequency among females than in males, especially among those who suffer from infertility (10).
Pericentric inversion of chromosome 9 is the most common type of inversion. It is considered to be a structural chromosomal variant in the general population usually without phenotypic effect. In this study we determined incidence of prenatal pericentric inversion of chromosome 9 in western region of Serbia and assess the perinatal outcomes of such fetuses.

2. MATERIALS AND METHODS

This study included a group of 949 pregnant women who underwent invasive prenatal diagnosis at the Department of Gynecology and Obstetrics in the General Hospital Uzice. Indications for prenatal diagnosis were age of pregnant women (over 35 years); results of biochemical analysis of fetal markers in maternal serum obtained by prenatal screening; genetic hereditary disease in the family; fetus or child born with multiple congenital anomalies; presence of balanced chromosomal rearrangements (reciprocal translocations, Robertsonian translocations, inversions) in one of the spouse. Amniocytes were obtained by puncture of the amniotic fluid of pregnant women in the 16-18-th week of gestation. Amniocytes were cultured in vitro for 10-20 days.
Chromosomes were isolated by standard techniques of preparation. After preparation, chromosomes were stained with the classical technique of staining and then analyzed under a light microscope. G-banded chromosomes were obtained by treating the slides with trypsin solution and stained in 4% Giemsa solution (Merck), dried and examined microscopically. Metaphases were karyotyped and interpreted according to the international system for human cytogenetic nomenclature (ISCN).

3. RESULTS AND DISCUSSION

In our work 949 amniocentesis were performed. This study included only patients in whom prenatal diagnosis using amniocentesis were performed at the Department of Gynecology and Obstetrics in the General Hospital Uzice. Total number of delivery during amounted to 14 950 including a group of pregnant women who underwent amniocentesis. In the examined time period on average about 7% of pregnant women were included invasive prenatal diagnoses. Indications for invasive prenatal diagnosis are 63% of cases were age of pregnant women (pregnant women older than 35 years), followed by 34% of abnormal findings of biochemical markers screening of the first and second trimester of pregnancy. A positive family history is an indication only in 3% of cases.
The age of the referred pregnant women ranged from 19-45 years, with a mean of 36.84 years. There was no significant correlation between the age of mother and pericentric inversion of chromosome 9 in fetus.
Using the G-banded technique among the 949 kariotypes, 24 (2.5 %) individual was found to have inversion of chromosome 9. Inversion of chromosome 9 was observed for 20 (83,3 %) female, while it was seen in 4 cases of males (16,7 %). Inversion of chromosome 9 discover in fetus karyotype during amniocentesis is shown on figures below (Fig. 1 and 2).
The incidence of inversion 9 in female fetuses was found significantly higher than that in male fetuses ($P< 0.05$). Similar higher frequency of inv 9 was revealed in female fetuses than in male in other literature data.
The pericentric inversion of the heterochromatic region of chromosome 9, inv(9), inv(9)(p11q13), or inv(9)(p12q13), is the most common pericentric inversion found in the human karyotype. Based on our study, the incidence of inversion of chromosome 9 is about 2,5 %, which corresponds to the values characteristic of this inversion in the general population (1-3 %).
Inv 9 is classified as a minor chromosomal rearrangement which does not correlate with abnormal phenotypes. Inversion of chromosome 9 has no phenotypic expression because it is affected by heterochromatic region. Despite this fact inv 9 is sometimes associated with increased chromosomal instability, congenital abnormalities, and cancer. In most cases with phenotype expression inversion 9 arised *de novo*. Unlike the inherited inv(9) found in normal populations, *de novo* pericentric inversions would be expected to have other cryptic genomic abnormalities. This may explain why *de novo* inv(9) is associated with various clinical features. Patients with de novo inversion 9 had dysmorphic features and/or congenital anomalies including: polydactyly, club foot, microtia, deafness, asymmetric face, giant Meckel's diverticulum, duodenal diaphragm, small bowel malrotation, pulmonary stenosis, atrial septal defect, tricuspid regurgitation, cardiomyopathy, arrhythmia, intrauterine growth restriction, and oligohydramnios

[11]. Analyses have shown that inv 9 in analyzed cases in our study did not arise *de novo* but were inherited from one parent mostly from mother. Phenotype of children in our study with prenataly diagnosed inv9 was normal.

3.1. Figures

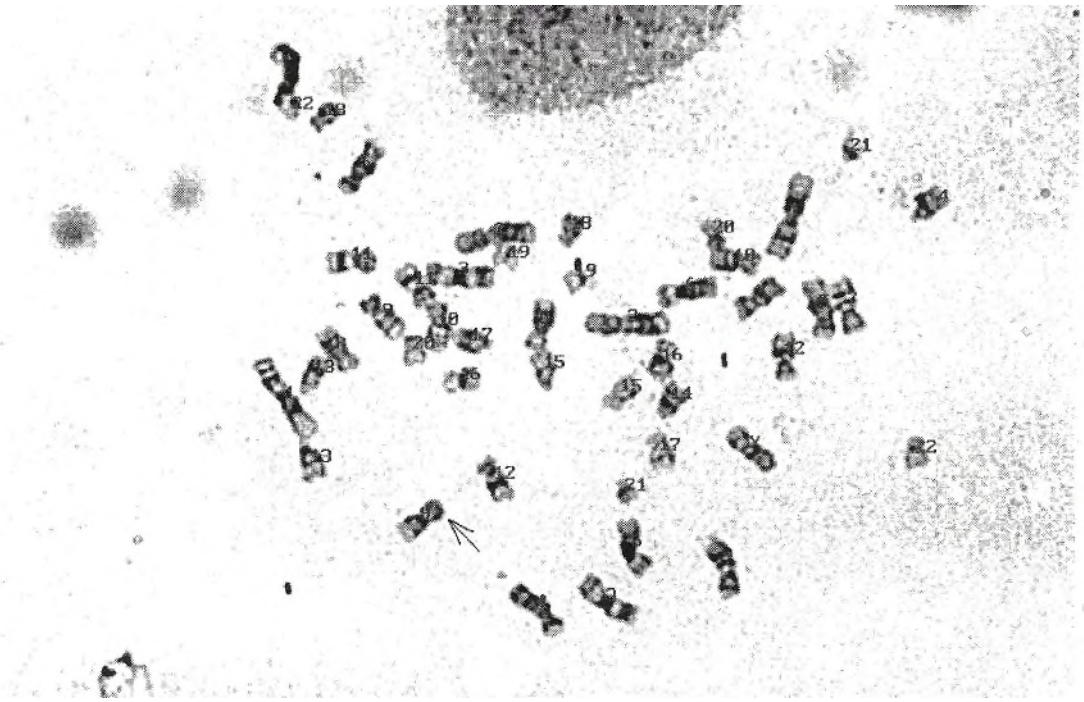

Figure 1: Fetus with inv9 methaphase

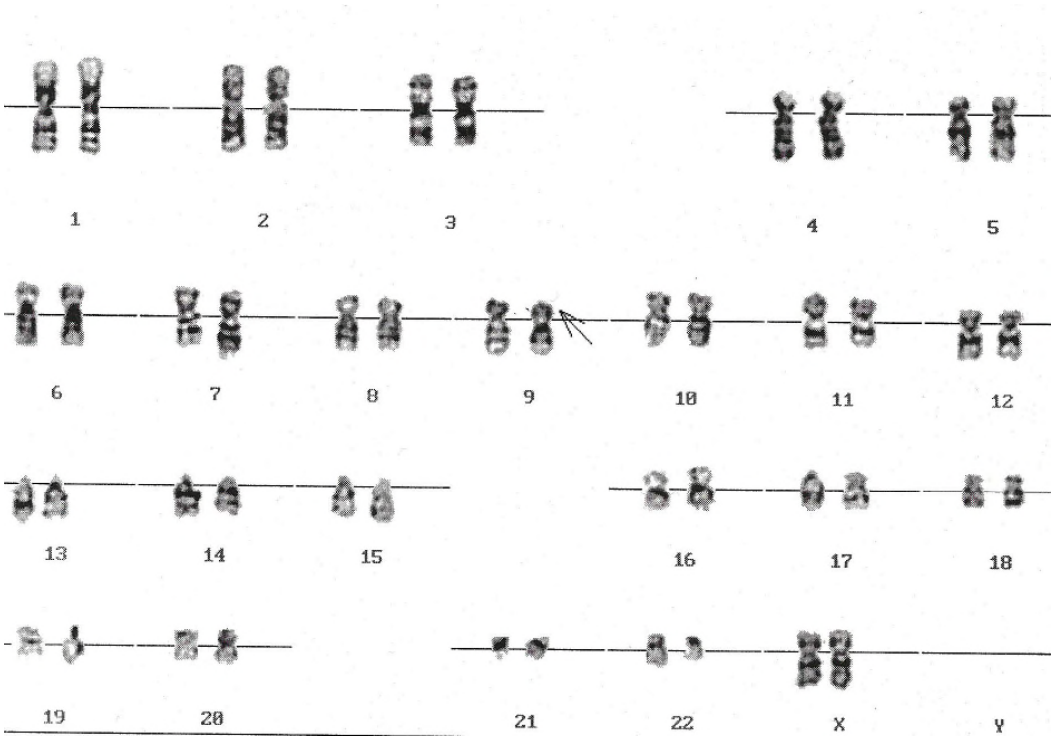

Figure 2: Fetus with inv9 karyotype

4. CONCLUSION

The incidence of the pericentric inversion of chromosome 9 in prenatal samples of population in western Serbia is in accordance with the expected incidence in the human population. Our data support the clinical reports that inversion of chromosome 9 is associated with a normal outcome.

[1] Gardner and Sutherland. *Chromosome Abnormalities and Genetic Counseling, 3rd Edition*. NY, NY: Oxford University Press; 2004.
[2]Gardner, R.J.M; Sutherland, Grant R.; Shaffer, Lisa G. (2011). "9 Inversions". *Chromosome Abnormalities and Genetic Counseling (4th ed.)*. Oxford University Press. pp. 161–182. *ISBN 978-0-19-974915-7*.
[3] Kim JW, Lee JY, Hwang JW, Hong KE. *Behavioral and developmental characteristics of children with inversion of chromosome 9 in Korea: a preliminary study*. Child Psychiatry Hum Dev. 2005;35:347–357
[4] Rao BV, Kerketta L, Korgaonkar S, Ghosh K. *Pericentric inversion of chromosome 9[inv(9)(p12q13)]: Its association with genetic diseases.* Indian J Hum Gent. 2006;12:129–132.
[5] Salihu HM, Boos R, Tchuinguem G, Schmidt W. *Prenatal diagnosis of translocation and a single pericentric inversion 9: the value of fetal ultrasound*. J Obstet Gynaecol. 2001;21:474–477.
[6] Keung YK, Knovich MA, Powell BL, Buss DH, Pettenati M. *Constitutional pericentric inversion of chromosome 9 and acute leukemia.* Cancer Genet Cytogenet. 2003;145:82–85.

[7] Yasuhara T, Okamoto A, Kitagawa T, Nikaido T, Yoshimura T, Yanaihara N, et al. *FGF7-like gene is associated with pericentric inversion of chromosome 9, and FGF7 is involved in the development of ovarian cancer*. IntJ Oncol. 2005;26:1209–1216.
[8] Kumar M, Thatai A, Chapadgaonkar SS. *Homozygosity and heterozygosity of the pericentric inversion of chromosome and its clinical impact*. J Clin Diagn Res. .
[9] Arun Muthuvel, Manipriya Ravindran, Aravind Chander, and Chandralekha Subbian *Pericentric inversion of chromosome 9 causing infertility and subsequent successful* in vitro *fertilization*. Niger Med J. 2016; 57(2): 142–144.
[10] Šípek A Jr, Panczak A, Mihalová R, Hrcková L, Suttrová E, Sobotka V, et al. *Pericentric inversion of human chromosome 9 epidemiology study in czech males and females*. Folia Biol (Praha) 2015;61:140–6.
[11] Jeong SY, Kim BY, Yu JE. *De novo pericentric inversion of chromosome 9 in congenital anomaly* Yonsei Med J. 2010;51(5):775-80.