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Ali Akbari, Nastaran; Tooba, Khatereh

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Analyzing indications of amniocentesis and positive predictive value (PPV) of cytogenetic findings of chromosomal abnormalities

Análisis de las indicaciones de amniocentesis y valor predictivo positivo (VPP) de hallazgos citogenéticos de anomalías cromosómicas

Nastaran Ali Akbari

Medical Department- Ardabil Branch-Islamic Azad

University - Ardabil-Iran, Irán

 <http://orcid.org/0000-0001-7888-721X>

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id=170263176011

Khatereh Tooba

Medical Department- Ardabil Branch-Islamic Azad

University - Ardabil-Iran, Irán

dr.kh.tooba@gmail.com

 <http://orcid.org/0000-0002-3022-0587>

ABSTRACT:

Analysis of the causes and extent of initial diagnosis by invasive method of amniocentesis is very important in order to investigate the chromosomal abnormalities and other severe congenital defects to provide genetic counseling of pregnant women. In Ardebil province (northwest of Iran), due to failures such as infertility, repeated abortion and embryonic anomalies, a study was conducted to analyze amniotic fluid samples of pregnant mothers, to determine amniocentesis indications, to determine the frequency and types of chromosomal abnormalities and adaptability of indication of amniocentesis in pregnant women. This retrospective descriptive-analytic study was conducted on all amniocentesis files (715 referrals to the only Amniocentesis Center of Ardebil province) over 2 years. Data were collected by examining the patients' file. The variables included: maternal age, indication of amniocentesis, chromosomal anomalies, and type of chromosomal abnormalities. After completing the data, the data were analyzed using descriptive and analytical statistics in SPSS software version 16. Data analysis showed that the most common cause of amniocentesis was a positive result in maternal serum screening (58.04%). Chromosomal abnormalities were observed in 5.5%. 56.4% of chromosomal abnormalities were the type of change in number (including trisomy 21) and 35.9% were the structural type. The inversion of chromosome No 9 was 33.3%. Among pregnant women, 78.7% had 1 indication, 20.6% had 2 indications, and 0.7% had 3 or 4 indications. The correlation between the results of amniotic fluid karyotype tests and serum tests was significant. The positive predictive value analysis showed that the more the number of indications is more; the positive predictive value tends to be maximized. Investigating indications and results of embryonic amniocentesis samples in the present study indicates the importance of genetic screening for the identification of chromosomal abnormalities in 5.5% of pregnant women. The most common indication and the main chromosomal abnormalities detected with amniocentesis in our region are from positive result in maternal serum screening and trisomy 21, which is consistent with the latest findings in this area in other countries, respectively.

The degree of adaptability of initial indication and the results of the amniocentesis genetic tests indicated that serum tests have undertaken a major contribution from the results for amniocentesis. In the analysis of indications, if the differentiation threshold regulated for invasive diagnostic tests is considered higher, probability of drift and the birth of babies with chromosomal defects will decrease.

KEYWORDS: Genetic disorders, Amniocentesis, Indication, Predictive value.

RESUMEN:

El análisis de las causas y el alcance del diagnóstico inicial mediante un método invasivo de amniocentesis es muy importante para investigar las anomalías cromosómicas y otros defectos congénitos graves para proporcionar asesoramiento genético a mujeres embarazadas. En la provincia de Ardebil (noroeste de Irán), debido a fallas como infertilidad, abortos repetidos y anomalías

AUTHOR NOTES

dr.kh.tooba@gmail.com

embrionarias, se realizó un estudio para analizar muestras de líquido amniótico de madres embarazadas, para determinar las indicaciones de amniocentesis, para determinar la frecuencia y los tipos de anomalías cromosómicas y Adaptabilidad de la indicación de amniocentesis en mujeres embarazadas. Este estudio retrospectivo descriptivo analítico se realizó en todos los archivos de amniocentesis (715 referencias al único Centro de Amniocentesis de la provincia de Ardebil) durante 2 años. Los datos fueron recolectados mediante el examen del expediente de pacientes. Las variables incluyeron: edad materna, indicación de amniocentesis, anomalías cromosómicas y tipo de anomalías cromosómicas. Después de completar los datos, los datos se analizaron mediante estadísticas descriptivas y analíticas en el software SPSS versión 16. El análisis de los datos mostró que la causa más común de amniocentesis fue un resultado positivo en la detección del suero materno (58.04%). Se observaron anomalías cromosómicas en el 5,5%. El 56,4% de las anomalías cromosómicas fue el tipo de cambio en el número (incluida la trisomía 21) y el 35,9% fue el tipo estructural. La inversión del cromosoma n° 9 fue del 33,3%. Entre las mujeres embarazadas, el 78.7% tenía 1 indicación, el 20.6% tenía 2 indicaciones y el 0.7% tenía 3 o 4 indicaciones. La correlación entre los resultados de las pruebas de cariotipo de líquido amniótico y las pruebas de suero fue significativa. El análisis del valor predictivo positivo mostró que cuanto mayor es el número de indicaciones, mayor es la cantidad; El valor predictivo positivo tiende a ser maximizado. La investigación de las indicaciones y los resultados de las muestras de amniocentesis embrionaria en el presente estudio indica la importancia del examen genético para la identificación de anomalías cromosómicas en el 5,5% de las mujeres embarazadas. La indicación más común y las principales anomalías cromosómicas detectadas con la amniocentesis en nuestra región provienen de resultados positivos en el cribado sérico materno y la trisomía 21, lo que coincide con los últimos hallazgos en esta área en otros países, respectivamente.

El grado de adaptabilidad de la indicación inicial y los resultados de las pruebas genéticas de amniocentesis indicaron que las pruebas de suero han realizado una importante contribución de los resultados de la amniocentesis. En el análisis de las indicaciones, si el umbral de diferenciación regulado para las pruebas de diagnóstico invasivo se considera más alto, la probabilidad de deriva y el nacimiento de bebés con defectos cromosómicos disminuirá.

PALABRAS CLAVE: trastornos genéticos, amniocentesis, indicación, valor predictivo.

INTRODUCTION:

Diagnosis of chromosomal abnormalities in the fetus is one of the most important challenges in modern perinatology. Among the most common chromosomal abnormalities in infants, it can refer to 21, 18, 13 trisomies, X monosomal and other Aneuploidy of sex chromosomes, which these aneuploidy can be considered live birth for up to 95% of chromosomal abnormalities¹. The only way to prevent the birth of infants with chromosomal abnormalities is prenatal diagnosis; these disorders are now diagnosed with screening tests that are a part of prenatal care around the world². The prenatal screening program identifies those women who are at high risk for the birth of a fetus with trisomy 21 or another major chromosomal abnormality. Protocols that are currently in use include screening serum markers, ultrasound scans, or a combination of these two methods. These screening tests put mothers at risk in two general categories; A group is low-risk individuals who does not require any other test, but the other group is those who, after measuring the biochemical markers and ultrasound are in the high-risk group, and it is suggested to these women to perform an invasive diagnostic test such as amniocentesis or sampling of chorionic villus, and to carry out karyotype from embryonic tissues³.

Amniocentesis as the most commonly used invasive technique that allows prenatal diagnosis of chromosomal abnormalities in pregnant women with a high risk of embryonic chromosomal abnormalities was first introduced in the 1960s; high diagnostic accuracy and very little risk of this method for embryos and mothers caused amniocentesis to become a gold standard for pre-natal diagnosis of genetic and chromosomal abnormalities. The most appropriate time to perform amniocentesis is 15 to 20 weeks of pregnancy (Middle three-month method or Mid-Trimester)⁵. The most important reason for amniocentesis in pregnancy is the evaluation of embryonic karyotype and the chromosomal examination of amniotic fluid cells. The most important indications for amniocentesis include: (1) high maternal age at pregnancy (35 years or older); (2) Presence of chromosomal abnormalities in previous pregnancies; (3) abnormal result of screening in the first or second trimester of pregnancy; (4) positive family history about a chromosomal or genetic disorder; (5) being carrier of parenting about one of the chromosomal abnormalities; (6) history of uterine infections or

Rh incompatibility^{6,7}. Generally, amniocentesis and chromosomal studies give valuable information about the chromosomal structure of the fetus; if the embryo has a natural chromosomal structure, pregnancy can be continued without concern, but if there is a chromosomal abnormality, the probability of the fetus to consequences associated with that abnormality, such as mental retardation and physical abnormalities, is high, in which case it is necessary to decide consciously whether to continue or discontinue pregnancy^{1,8}.

Zhang et al.⁹ in a study in 2017 in China have investigated and analyzed embryonic chromosomal abnormalities through amniocentesis. In this study, the results of genetic analysis of 40208 fetuses were evaluated by amniocentesis indication. Among all these samples, the positive test for serum maternal screening was the most common indication for amniocentesis (17536 cases; 43.67%). Abnormal karyotype diagnosis rate, if one of the couples had chromosomal anomalies was 55.60%, in pregnant women with pathological findings of ultrasound was 4.43%, in pregnant women with high age was 2.83% and in women with abnormal serum screening was 2.73%. Of the embryos with chromosomal abnormalities, 680 cases (50.41%) had trisomy 13, trisomy 18 or trisomy 21, and 138 cases (10.23%) had sex chromosome disorder. Other 531 abnormal samples included displacement anomalies, mosaicism, inversion, removal, increase, and marker chromosome.

Ozcan et al.¹⁰ in a study in 2017 investigated and analyzed chromosomal abnormalities in 2185 pregnancies in Turkey. The main indication for amniocentesis was abnormal aneuploidy results for trisomy 21, then older maternal age, and embryonic structural abnormalities.

Chang et al.¹¹ in a study in Taiwan in 2016, investigated chromosomal abnormalities among 31,556 amniocentesis cases. The findings of this study showed that 3 common indications for amniocentesis were high maternal age (75.11%), abnormal result of serum maternal screening in the second trimester (13.22%), and abnormal ultrasound findings (8.00%). Down syndrome was the most common autosomal abnormality (25.74%). Turner syndrome was the most common sex chromosome abnormality (7.04%). Of structural anomalies, 26.93% were balanced displacements and 17.10% were unbalanced displacements. The largest part of embryonic chromosomal abnormalities was found in cases where parents were also affected by chromosomal abnormalities (38.02%).

Mademont-Soler et al.¹² in a study in 2011 investigated the results of amniotic fluid samples. In this study, the results of the analysis of 29,883 amniotic fluid samples were investigated. The incidence of chromosomal abnormalities was 2.9%. In the meantime, 48.1% had classical autosomal aneuploidy that trisomy 21 was the most common. The main indications for amniocentesis, prenatal screening test and maternal age were high. The reasons for referring pregnant women to amniocentesis with the highest positive predictive value were increased thickness of the fluid behind the neck of fetus (9.2%) and ultrasound abnormalities (6.6%).

Nishiyama et al.¹³ in a study in 2015 in Japan investigated the frequency and type of abnormal karyotype in 28,983 amniotic fluid samples collected before the 22nd week of pregnancy. This study was conducted at the national level and retrospectively. Abnormal karyotype occurrence was 6%.

Given that chromosomal abnormalities are one of the main causes of congenital severe defects, it is evident that the study and analysis of amniotic fluid samples and the occurrence and type of chromosomal abnormalities has a great importance for the genetic counseling of pregnant women; The numerous studies that have been carried out in recent years in this field show the importance of studying in this regard⁹⁻¹³; however, in the region, there are no previous studies on frequency and abnormal type of karyotype in the region's population identified with amniocentesis. The aim of this study was to investigate and analyze the amniotic fluid samples of pregnant mothers in Ardabil, to determine amniocentesis indications, to determine the frequency of anomalies, to determine the type of chromosomal abnormalities, and to determine the types of chromosomal abnormalities among pregnant women and the degree of adaptability of amniocentesis among pregnant women.

Research Method:

This retrospective descriptive-analytic study was conducted on all amniocentesis files (715 referrals to the only Amniocentesis Center of Ardebil province) over 2 years. Data were collected by examining the patients' file. The variables included: maternal age, indication of amniocentesis, chromosomal anomalies, and type of chromosomal abnormalities. Positive predictive value (PPV) was calculated based on the degree of adaptation of the initial diagnosis based on the indications and the result of cytogenetic tests of the samples was calculated from the amniotic fluid.

After completing the data, the data were analyzed using descriptive and analytical statistics in SPSS software version 16. To analyze the data, descriptive statistics methods including classification of information, conversion of classified information to frequency table, setting frequency percentage and drawing diagram were used. In order to adapt, Chi square test and ratio test was used.

Amniocentesis indications among pregnant women:

Figure 1 shows the amniocentesis indications among pregnant women studied. It is observed that among 715 pregnant women, who were under amniocentesis, 78.7% had 1 indication, 20.6% had 2 indications, and 0.7% had 3 or 4 indications. Meanwhile, the most common cause of amniocentesis was a positive result in maternal serum screening (58.04%). Other common causes were as the following: positive result in serum maternal screening and increasing Nuchal Translucency(11.5%); self-patient's request (4.9%); increasing Nuchal Translucency(4.62%); And abnormal findings in ultrasound (3,78%). Table 1.

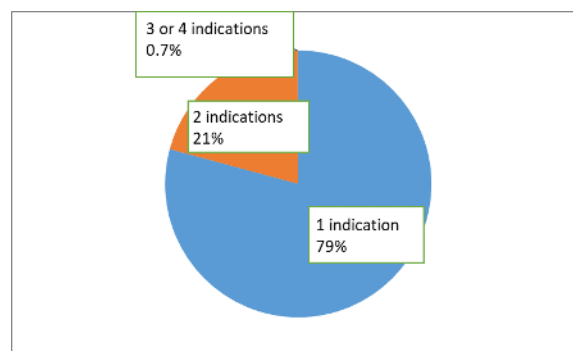


FIGURE 1
Frequency of amniocentesis indications among pregnant women

TABLE 2
Amniocentesis indications among pregnant women

Percent	Indication	
58.04%	Positive result in maternal serum screening	
4.90%	Patient's request	
4.62%	increasing Nuchal Translucency	
3.78%	Abnormal findings in ultrasound	
2.80%	Bad obstetric history (previous history of abortion, history of stillbirth or neonatal death, anomaly)	1 indication
0.84%	Mother's high age (over 35 years old at birth)	
1.40%	Parent chromosomal abnormalities	
2.38%	No Indication	
11.05%	Positive result in maternal serum screening + Increasing Nuchal Translucency	
3.22%	Positive result in maternal serum screening + high maternal age	
1.96%	Positive result in maternal serum screening + Parental chromosomal abnormalities	
1.40%	Positive result in maternal serum screening + Abnormal findings in ultrasound	
0.84%	Positive result in maternal serum screening + bad obstetric history	
0.28%	High maternal age + Abnormal findings in ultrasound	2 indications
0.14%	High maternal age + Increasing Nuchal Translucency	
0.14%	High maternal age + Parental chromosomal abnormalities	
0.14%	High maternal age + bad obstetric history	
0.98%	Abnormal findings in ultrasound+ Increasing Nuchal Translucency	
0.28%	bad obstetric history+ Abnormal findings in ultrasound	
0.14%	bad obstetric history+ Increasing Nuchal Translucency	
0.28%	Increasing Nuchal Translucency+ Abnormal findings in ultrasound+ Abnormal findings in ultrasound	
0.14%	Positive result in maternal serum screening + bad obstetric history+ Increasing Nuchal Translucency	3 or 4 indications
0.14%	Positive result in maternal serum screening + Abnormal findings in ultrasound + Increasing Nuchal Translucency	
0.14%	Positive result in maternal serum screening + bad obstetric history+ Parental chromosomal abnormalities+ Increasing Nuchal Translucency	
100%	Sum	

Frequency of chromosomal abnormalities among pregnant women:

Among 715 pregnant women who were under amniocentesis, chromosomal anomalies were 5.5% (Fig. 3).

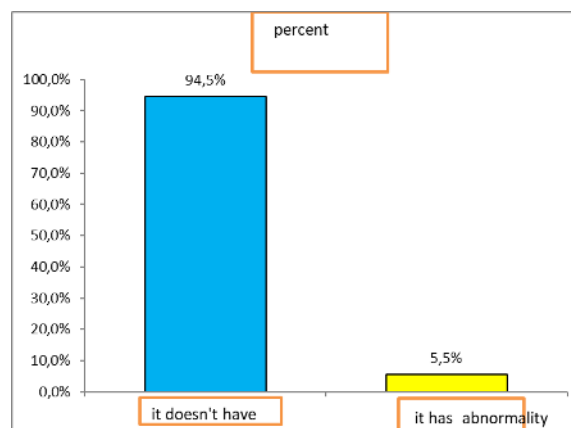


FIGURE 3
Frequency of chromosomal abnormalities among pregnant women

Chromosome abnormalities among pregnant women:

Among the studied samples with chromosome anomalies, 56.4% were numerable type and 35.9% were structural type; also, 7.7% were chimeric (Table 3).

A variety of chromosomal abnormalities is inserted in cases with abnormalities in Table 3. In general, the most common abnormality is trisomy 21 (35.9%), and then, the inversion of chromosome number 9 (33.3 Percent). Other abnormalities are as follows: Chimera (7.69%), translocation (5.13%), and then trisomy 18, trisomy 13, Klinefelter's syndrome, mosaicism Klinefelter's syndrome, Turner syndrome, Trisomy 21 mosaicism, and Triple X syndrome of mosaicism (each of which is 2.56%).

TABLE 3.
Chromosome abnormalities among pregnant women

Karyotype	Percent	Abnormality	
7 cases (47, XX, +21)	35.90%	Trisomy 21	Numerable
7 cases (47, XY, +21)			
45, XX, reln (13;14)	2.56%	Robertsonian Translocation	
46, XY /47, XY(+21)	2.56%	Trisomy 21 mosaicism	
47, XY, +18	2.56%	Trisomy 18	
47, XY, +13	2.56%	Trisomy 13	
47, XXY	2.56%	Klinefelter	
47, XXY/46, XY	2.56%	MosaicismKlinefelter	
45, X	2.56%	Turner syndrome	
46, XX/47, XXX	2.56%	Triple X syndrome of mosaicism	
8 cases (46, XX, inv(9)) 5 cases (46, XY, inv(9))	33.33%	The inversion of chromosome 9	Structural
46, XX, t(7p/14p)	2.56%	Interchange	
46, XX/46, XY	7.69%	Chimera	
-	100%	Sum	

Chromosomal abnormalities among pregnant women are shown in Table 4 in terms of indications of amniocentesis. Investigating diagnostic indications indicates that the positive result in the mother's serum screening was the highest indication for the initial diagnosis and was almost a good indication for most chromosomal abnormalities. Inversion of chromosomes had a high frequency, which was firstly diagnosed

observed that the reported range for frequency of chromosomal abnormalities detected with amniocentesis in different countries is between 2.42% and 6%, which our study's finding is in this range.

Our study findings about the causes of amniocentesis showed that the most common indication was the positive result in maternal serum screening, which the cause of more than half of the amniocentesis cases in our population was formed by this indication (58.04%). The most common indication of amniocentesis in studies by Zhang et al.⁹ in China and Mademont-Suler et al.¹² in Spain was also the positive result in maternal serum screening (43.7% and 44.1% of all items) that match our findings in this respect.

But the most common cause of amniocentesis in studies by Chang et al.¹¹ in Taiwan and Nishiyama et al.¹³ in Japan has been reported high maternal age that are different from our study. It should be noted that in the early years of the introduction of amniocentesis as a prenatal cytogenetic diagnostic tool, "high maternal age" was the main cause of reference for amniocentesis, since positive association between embryonic aneuploidy and maternal age was well specified^{28,29}.

Today, however, the high maternal age is considered as an unconventional separate criterion¹², and biochemical markers such as serum alpha-fetoprotein levels, Human Chorionic Gonadotropin, and Pregnancy-associated plasma protein A associated with maternal age reach a high rate of identification for Chromosomal abnormalities³⁰. In our study, "high maternal age" was considered only as a single indication of amniocentesis in only (0.84%) of pregnant women, while in 28 other cases with causes, such as "positive result in maternal serum screening", "Abnormal findings in ultrasound", "Increasing Nuchal Translucency", "Parental chromosomal abnormalities", and "Bad obstetric history" was raised as an indication of amniocentesis.

In the present study, the prevalence of numerical chromosomal abnormalities was higher than structural abnormalities (56.4% vs. 35.9%). In all previous studies, the prevalence of numerical chromosomal abnormalities has been reported more, including in Zhang et al.⁹ in China, 63.1% of the abnormalities were the numerical type and 36.99% were the structural type; In Chang et al.¹¹, in Taiwan, 56.5% of abnormalities were the numerical type and 43.5% were the structural type; in Chang Mademont-Suler et al.¹² in Spain, 61.3% of abnormalities were the numerical type and 26.2% were structural type and in the study of Nishiyama et al.¹³, in Japan, 65.6% of the abnormalities were numerical type and 18.4% were the structural type.

In addition, the most common abnormality among all the chromosomal abnormalities observed in the women studied in this study was trisomy 21, which included 35.9% of all cases. Similar to our study, in the study of Ozjan et al.¹⁰ in 2017 in Turkey, trisomy 21 was the most common aneuploidy. Also, in other similar studies, trisomy 21 has been reported as the most common chromosomal abnormalities, including studies by Chang et al in Taiwan (with a frequency of 25.74%), Zhang et al.] in China (with a frequency of 37.44%), Mademont-Suler et al in Spain (with a frequency of 37.9%), and Nishiyama et al.¹³ in Japan (with a frequency of 43.5%).

It is observed that our finding that trisomy 21 is the most important chromosomal abnormality detected with amniocentesis is consistent with results of other studies and support them. In general, Trisomy 21 (Down syndrome) is clearly the most common and most known chromosomal abnormality that affects nearly one in every 800 live births to Down syndrome. The syndrome was first clinically described by Langdon Down in 1866, and in 1959, it was found that most affected children have 47 chromosomes (additional chromosomes 21). Studies show that a high percentage of pregnancies with Trisomy 21 abort spontaneously and only about 20-25% of these pregnancies survive until birth. About a quarter of live births have heart defects that die before they are one year old. Among the babies who survive, the risk of leukemia and blood cancers increases 12 times. Also, among survivors, the risk of Alzheimer's and dementia increases to a very high rate³¹.

The second most common chromosomal abnormality in the present study, which was under amniocentesis, was inversion of chromosome 9 (33.3%). The prevalence of inversion abnormality in studies by Mademont-Suler et al.¹² in Spain was 7.5 percent, Nishiyama et al.¹³ in Japan, 3.8 percent, Chang et al.¹¹ in Taiwan, 22.10 percent, and Zhang et al.⁹ in China was reported 4/3 percent which is less than our study. Chromosome inversion 9 is a recombinant that may be accidentally reported in well-healthy individuals. Its prevalence in the general population is 1-1.65%. Despite the categorization of this recombinant as a small chromosomal disorder and its lack of association with abnormal phenotype, many reports indicate its relation with reducing fertility, frequent abortion, increasing chance of chromosomal abnormalities, and intrauterine fetal death. The incidence of this disorder is not related to the gender, as well as the reduction in fertility in 36% of those who carry the inversion of chromosome 9 can be seen¹⁵⁻¹⁹.

Investigating indications and results of embryonic amniocentesis samples in the present study indicates the importance of genetic screening for the identification of chromosomal anomalies in 5.5% of pregnant women. Our study also showed that the most common indication and the most important chromosomal abnormalities detected with amniocentesis is the positive result in maternal serum screening and trisomy 21, which is consistent with the latest findings in this area in other countries. Our findings can provide useful information for the genetic counseling of pregnant women in Ardabil, and it is recommended that in the analysis of indications, instead of selecting 1% of those who are at risk for amniocentesis; its contribution should be considered more as some countries. In the analysis of indications, if the differentiation threshold regulated for invasive diagnostic tests is considered higher, the probability of drift and the birth of infants with chromosomal defects will decrease.

Given the results of the karyotype of amniocentesis samples and the comprehensive assessment of embryo development with ultrasound, genetic counseling can inform parents about the clinical outcomes of anomaly and therapeutic options and guide them to continue pregnancy or end it according to the law.

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